The Electrophysiology of Face Perception in Williams Syndrome

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Abstract

Williams Syndrome is a rare genetic disorder in which the processing of faces and visual 'perception' has been argued to be intact despite other 'deficits' of visuospatial processing. In contrast, the theoretical approach taken in this thesis argues that the brains of those with developmental disorders cannot be legitimately viewed in terms of sparing and impairment, but must be considered as having atypical properties emergent as a result of atypical development. The event-related potential technique is used to provide evidence of abnormalities of perception of visual stimuli, including faces, even within the first 250ms of processing. A new approach to the brain imaging of people with developmental disorders is discussed. The thesis concludes by proposing an 'abnormal binding' hypothesis which aims to explain the nature and neural basis of the visuo-cognitive processing abnormalities in Williams Syndrome.

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Introduction

Introduction

The work presented in the current thesis was motivated by a new theoretical approach to imaging developmental disorders, described in detail by Johnson and colleagues (Johnson, Halit, Grice & Karmiloff-Smith, In Press). As outlined below, it is based on an 'interactive specialisation' (Johnson, 2000) view of typical development which is then applied to the atypical case. The result is that the currently popular application of the adult neuropsychology model is rejected in favour of the neuroconstructivist approach to developmental disorders (Karmiloff-Smith, 1998). This has some important consequences for the topic of enquiry and the methods used.

Maturational View

All developmental disorders could be studied with the neuroconstructivist approach, but one, Williams Syndrome (WS), is of particular interest because of an unusual imbalance in cognitive profile. Research on cognition in this disorder has been influenced by two views of typical development, the 'maturational' and the 'interactive specialisation' (IS) approaches, which vary in the relative weight given to genetic predeterminism versus probablistic epigenisis. The first approach, historically speaking, is governed by a (largely implicit) 'experience-independent' view of typical development, whereas the IS approach regards experience as critical. For proponents of the maturational account, genetic information determines brain development such that the functioning of cognitive mechanisms is, to a great extent, pre-specified. Cognitive development is characterised as the maturing of domain-specific modules that unfold over time as the individual grows. For example, the assumption of genetically specified modularity of visuospatial ability has propelled research on Williams Syndrome. One of the genes which is typically deleted in WS is LIMK1 (Frangiskakis, Ewart, Morris, Mervis, Bertrand et al., 1996; Tassabehji, Metcalfe, Fergusson, Carette, Dore et al., 1996) and one of the areas of poorest functioning in the disorder is visuospatial cognition (see Chapter Two). For researchers such as Frangiskakais and colleagues, there is thought to be a clear

genotype-phenotype relationship such that the haploinsufficiency of LIMK1 results in the loss of visuospatial ability.

In research on the typical development of face processing, the probabilistic epigenesis versus genetic predeterminism debate has been (simplistically) interpreted as reflecting the distinction between a domain-general mechanism for expert subordinate classification and a domain-specific innate mechanism for the processing of faces alone. The most influential of such views of brain development is the modularity approach of Fodor (Fodor, 1983), which fits into the latter camp. According to Fodor, a module is a specialised mental mechanism that has 'evolved' to process 'specific information types' which are particularly relevant to a species.

A huge body of work has accumulated to assess the modularity of face processing in the typical case, although it often neglects Fodorian terminology and instead is directed at the 'specialness' debate. Most studies of face processing aim to find out if faces are a special class of visual stimuli by their focus on three questions. First, is there a part of the brain *specific* to face stimuli? Second, is the processing of faces unique (since it is possible for a separate mechanism to exist which is not *qualitatively* different from that for object recognition)? Third, and most recent, does face recognition change over development (do all individuals go through the same developmental stages which are different to those for object processing)? These research questions map directly onto three of Fodor's nine criteria for module classification:

- 'Localisation'
- 'Domain specificity'
- 'Ontogenetic universals'

In other words, modules are thought to be genetically specified cognitive systems that depend on dedicated neural circuitry, exclusively process one type of information, and develop in a characteristic sequence across individuals.

The unusual cognitive profile of Williams Syndrome has been used to support the Fodorian view (see Chapter Two). People with WS are usually remarkably good at face recognition, despite their poor visuospatial skills. This surprising imbalance in performance has been popularly explained with reference to the innate specification of cognitive modules. In short, as already described, the belief is that the genes for successful visuospatial performance are knocked out in the disorder. However, the assumption is also that the genetic codes for the face processing module remain intact. The experiments presented in Chapters Six to Nine of the current thesis constitute an investigation of such claims, and assess the contribution that WS research could make to alternative theories of cortical organisation.

The view that there is a direct causal link from genotype to phenotype results in at least three assumptions when applied to the neuroimaging of developmental disorders, the localisation, the static and the deficit assumptions (Johnson et al., In Press). The 'localisation' assumption claims that there is a direct mapping between the loss or damage of a particular brain structure and the functioning of the associated cognitive mechanism. In other words, neuroimaging should be able to localise the seat of damage. The converse is also true (though rarely researched directly). The static assumption states that if a cognitive module, such as face processing, is 'intact' then neuroimaging studies should reveal the existence of a normal face processing mechanism. In addition this 'normality' should hold throughout development. In other words, the gene to brain to cognition / behaviour relationship should remain unchanged as the individual grows, i.e., once a brain area is 'mature' it will remain constant in function. Finally, the 'deficit' assumption states that the relationship between the brain mechanism and cognition is uni-directional as the brain deficit is thought to cause the deficits at the cognitive and behavioural levels. Behaviour itself should in no way change the module in the brain. Logically this argument must also hold for 'intact' mechanisms and the typical case. For example, repeated experience with human faces should not play a causal role in the progressive modularisation of face processing; face experience should simply trigger the operation of a face processing module.

Interactive Specialisation

One alternative to the genetic predeterminist approach has been discussed in relation to Williams Syndrome (Karmiloff-Smith, 1998). This is based on a probabilistic view of epigenisis (Gottlieb, 1992) called 'interactive specialisation' (Johnson, 2000). The assumptions underlying the interactive specialisation approach can be directly contrasted with those of the maturational view and result in very different predictions for the neuroimaging of developmental disorders (Johnson et al., In Press). Proponents of interactive specialisation claim that, in addition to the effects of genetic predisposition, the anatomy of the cortex is dependent on activity within and between different brain areas. This is a view in which innate architectural constraints on the cortex are characterised in terms of connectivity between brain structures, and biases in favour of certain kinds of information processing (Elman, Bates, Johnson, Karmiloff-Smith, Parisi et al., 1996). Development is seen as probabilistic. In other words, innate biases like synaptic density or connectivity (which can be conceptualised as weights or activation functions in the nodes of a neural network), exist in different sets of brain areas which make them more likely to be recruited for certain functions (Elman et al., 1996). However, 'areas' are likely to be large-scale and bias is likely to exist in terms of a gradient. For example, synapses could be relatively more dense at area X than Y, but gradually increase between X and Y. So genetic information that affects 'bias' is likely to be expressed over the whole cortex (just a relatively larger effect at X than at Y). In relation to syndromes involving mutation of such genes, this means that there will not be discrete effects at one particular cortical region but widespread effects that are more obvious in some regions than in others (Karmiloff-Smith, 1998).

For the neuroconstructivist, development involves progressive modularisation of areas of cortex such that they eventually *become* specific for processing only a small selection of the initial inputs (Karmiloff-Smith, 1992; Elman et al., 1996). For example, general mechanisms for visual perception could become progressively modularised for face processing due to both initial constraints and repeated experience with faces. This does not mean, however, that particular functions can

necessarily be localised within a particular area. Connectivity and temporal correlation between cortical regions are hypothesised to be as important. Neural networks consisting of collaborating but spatially separate computational components can be responsible even for the activity of developing cognitive modules. So what the process of modularisation may actually involve is the re-organisation of connectivity between anatomical areas. The assumption is that, even when a cortical region has reached 'maturation', its function may not be constant but may undergo a protracted course of change.

There is some evidence to support the neuroconstructivist approach, particularly in relation to the neuroimaging of face processing. As will be discussed in Chapter One, the N170 ERP is face sensitive. However, the equivalent component does not show evidence of such specificity in young infants. For example, early in development the N170 equivalent is not changed by face inversion. In addition, when viewing faces, both left and right hemispheres are active in infants, as opposed to the right hemisphere bias found in most adults (de Haan, Oliver & Johnson, 1998). These differences are not consistent with a maturational view of development, since fundamental changes should not occur in the function and cortical-lateralisation of a pre-determined module. They argue, by contrast, that brain development involves changes in areas of activation, becomes modularised and specialised over time and is affected by experience (see Chapter One for further discussion).

In relation to the imaging of developmental disorders, the neuroconstructivist assumptions contradict those of the maturational approach. The search for discrete localisable damage, static cognitive and brain mechanisms, as well as uni-directional effects from brain to cognition, is thought to be erroneous. The neuroconstructivist approach predicts that there will be no gross abnormality in any discrete brain region of an individual with a developmental disorder such as WS (Karmiloff-Smith, 1998). Instead, abnormalities will be more subtle and widespread, and may be more evident in the co-activity of neural regions compared to controls. The prediction is that the

WS brain develops along a different developmental trajectory. This means that domains of strong as well as weak performance should be investigated. Even in successful domains, the prediction is of differences in cognitive and cortical processing (Karmiloff-Smith, 1998). Evidence of any abnormality may also vary over the developmental span – it is not static. For example, infants may show no indication of a particular abnormal function evident in the adult end-state (Paterson, Brown, Gsodl, Johnson & Karmiloff-Smith, 1999). Neuroconstructivism, then, predicts that sampling longitudinally or in cross-section across infancy through to adulthood will prove vital. Finally, the approach predicts that experience is essential to brain development. Different kinds of pre-natal or post-natal experience, resulting in different kinds of brain activity, will result in different functional neuroanatomy.

Chapter One of the present thesis begins with an introduction to face processing and electrophysiology, where current issues regarding specialisation of function in typical development are discussed. This is followed by an outline of the genetics and neurophysiology, and cognitive profile of Williams Syndrome (Chapter Two). ERP methodology and related issues are then explained (Chapter Three) before the four main experimental chapters are presented (Chapters Four to Seven). The final chapter (Chapter Eight) discusses the inital research questions in light of the experimental results, and concludes with suggestions for further study.

Chapter One

Face Processing

1 Face Processing

Face processing can be broadly viewed as involving two stages, 'early' and 'late': the early stage includes detection of the face as a face and encoding of the structural properties of the face, and the later stage includes the recognition of identity and the accessing of semantic information about the face. While the face recognition of people with Williams Syndrome has been investigated in some detail, the detection / encoding stage has received less attention. This lack of investigation is not confined to WS research. Until recently, the majority of behavioural face processing studies focused on the later stages of recognition involved in identifying individuals. The earlier processes of detection and encoding, even in the most popular model of face processing (Bruce & Young, 1986), were subsumed into one pre-recognition 'structural' processing stage. However, recent evidence from a number of sources has indicated that early processing merits further investigation. These sources are considered in turn below. This chapter aims to illustrate what they reveal about how 'structural encoding' should be characterised (in the endstate, and over development) and how some aspects of its functioning might be measured by utilising electrophysiological techniques. The following chapter discusses how the study of one element of structural encoding (the encoding of configuration) may inform our knowledge about brain development, in Williams Syndrome and in the typical case.

1.1 Domain Specificity

1.1.1 The Inversion effect

To support claims about the domain specificity of face processing, a qualitatively different kind of processing must be found for faces compared to other non-face stimuli. The 'inversion effect' is the most important finding in cognitive research on face processing for this reason. When faces are turned upside down, identity recognition by typical adults significantly decreases and reaction time increases

(Yin, 1969). The recognition decrement for faces is disproportionately higher than that found for other classes of stimuli such as planes, houses, landscapes, and cars (Valentine, 1988). The effect has been tested using a number of different paradigms, including studies of matching, discrimination, and recognition memory with and without the explicit requirement for mental rotation (e.g. faces presented upright at study and test, versus upright at study and inverted at test (Valentine, 1988)). Some paradigms, especially those that require mental rotation, have been found to induce a larger inversion effect than others (Valentine & Bruce, 1986).

Until recently, it was unclear whether face inversion was disruptive early or late in the processing stream. Different processing stages, from encoding through to memory retrieval, were not systematically investigated using the same stimuli. However, this question (and the question of *what* is encoded, see below) has now been addressed by Freire and colleagues (Freire, Lee & Symons, 2000). They report four experiments in which different tasks were used. The first task involved discrimination between two photographs of faces in either the upright or inverted orientation, in order to make a same / different judgement. This was compared to the results of a delayed match-to-sample task using the same stimuli, in which the memory component was set at three different intervals. They found that the inversion effect was no different for the discrimination compared to the memory task, and that there was no effect of delay on the size of the inversion decrement. These results suggest that it is encoding that is significantly affected by inversion. As a consequence, Freire et al. claim that the inversion effect should be considered to be a 'perceptual' rather than a recognition phenomena.

1.1.2 What is encoded?

The face inversion effect has been explained with reference to the homogeneity of the gross configuration of faces, and the unusual level of categorisation required for recognition. Most theories of visual object processing suggest that objects are recognised by part decomposition, followed by analysis of the differences in the arrangement of these parts (Marr, 1982). This is adequate for distinguishing, for

example, chairs from faces. It is inadequate for fine discrimination between exemplars of largely homogenous stimuli like faces. In other words, all faces share the same basic spatial arrangement of parts with two eyes, nose, mouth, chin etc. Recognition of this prototypical pattern is enough to identify that a face is a face. However, in ordinary circumstances it is essential to attribute an individual identity to the face. Unlike most other classes of visual stimuli (e.g. chairs, plates, etc), the recognition of faces requires fine within-category individuation.

The distinction between the information available from a face compared to other objects, and the roles that different types of information play, have been long debated in the literature. A number of researchers have attempted to define, amidst some controversy, the properties of the different informational levels. Carey and Diamond (Carey & Diamond, 1977; Diamond & Carey, 1977; Diamond & Carey, 1986; Carey, 1992) describe 'featural information', comprising the facial elements like the eyes, nose and mouth. This is opposed to first and second order 'relational information', the former referring to the prototypical spatial arrangement of parts, and the latter referring to the specific spatial relationships (distances) between the parts of an individual face. The most commonly used dichotomy, however, is featural (also called analytic), versus 'configural' processing. Here, configural refers to a rough interpretation of second order relational information, as the spatial relationships between the face parts. In the recent Freire et al. study (Freire et al., 2000), described in the previous section, configural and featural information was independently manipulated (as much as it is possible to do so). In the feature change experiment, eyes, nose and mouth features were swapped between faces. For the configural change experiment, the eyes, nose and mouth were moved slightly such that the spatial relationships between parts changed. When inverted, the performance of participants discriminating configural changes dropped from 81% to 55% accuracy, whereas those discriminating feature change faces showed no change in performance (91% vs 90%). In comparison to the ability to percieve changes to inverted features, the perception of configural information is grossly disrupted by inversion.

The significance of configural information has been demonstrated in countless experiments. A good example is the 'Margaret Thatcher' illusion described by Thompson (Thompson, 1980). Thatcher's eyes and mouth are cut out and replaced on to the face upside down. When the resulting picture is viewed in the normal orientation the face appears grotesque, yet when the picture is inverted nothing about it appears abnormal. The relationship between features, which is so important to upright face recognition, is lost when the same face is viewed in the opposite orientation. Featural information does not appear to be orientation dependent to the same extent. In a different study, local changes to face features, which do not affect configural information (e.g. blacking out teeth), have a consistently 'grotesque' effect regardless of orientation (Searcy & Bartlett, 1996).

Inversion is the most common method for disrupting configural encoding, but the primacy of this processing over that of individual features can also be experimentally manipulated by using composite faces (Young, Hellawell & Hay, 1987). People are reasonably accurate at recognising the identity of familiar individuals when only presented with only the top half of the face. However when two halves (top and bottom) of different faces are aligned they produce a novel 'composite' whole face which interferes with recognition of the familiar half. This is not the case if the two halves are slightly mis-aligned, in which case recognition remains unimpaired. In fact configural context can both impair and facilitate recognition. People are quicker to recognise a particular feature (like a nose) of an individual when presented in the correct configural alignment, than when presented in a face outline in which the features have been scrambled (Tanaka & Farah, 1993).

Despite the predictive and explanatory power of the configural versus featural hypothesis, some have argued for alternative explanations of the face inversion effect. Valentine and Bruce (Valentine & Bruce, 1988), for example, argue that inversion adds noise to the encoding process (a quantitative rather than qualitative difference between upright and inverted representations), which affects both

configural and featural information. They attempted to test each hypothesis by its predictions of slope of recognition accuracy, and Reaction Time (RT), plotted against degree of deviation (up to 180 degrees) from the upright face. Results showed linear slopes, which cannot be accounted for by a qualitative shift (featural / configural) model. However, as acknowledged by the authors, their procedure may not have been sensitive enough to detect a processing shift. Murray, Yong & Rhodes, (2000) retested the hypothesis, adjusting to the sensitivity of the procedure by asking for perceptual ratings at the time of encoding, rather than relying on a memory component. Using this method, evidence of a qualitative shift in processing between 90 and 120 degrees is found, which offers no support to the 'noise' hypothesis.

1.2 Expertise

Recognition of individual faces, as already outlined, differs from the processing of other stimuli due to the level of categorisation required. It is not enough to encode the prototypical face configuration and deduce that a face is a face; humans are constantly required to individuate among a huge variety of face exemplars. In other words, humans are expert at identifying faces, and not most other categories of stimuli, at the subordinate level. This provides a potential confound for any study attempting to assess whether face recognition is carried out by domain-specific or domain-general mechanisms. Faces could be recognised by face specific mechanisms or by mechanisms specialised for subordinate categorisation (which is only usually required for faces), yet it is difficult to test because only faces and not most other potential comparison stimuli are expertly individuated at this level.

A critical study by Diamond & Carey (Diamond & Carey, 1986) illustrates the importance of considering 'expertise' effects on recognition. The inversion effect on recognition of human faces and of dogs was studied in naive participants compared to dog 'judges' with over ten years of experience of discriminating among dogs at the subordinate level. Individual dogs within a particular breed, like faces, differ in both individual distinguishing features and in configuration. The dog experts, unlike

the naive participants (who suffered a recognition decrement only to inverted faces), displayed an inversion effect for both faces and dogs. Diamond and Carey explain this effect in terms of a qualitative shift in processing with expertise. Dog judges recognised the dog stimuli by way of subtle changes in configuration, which was then disrupted by inversion. In contrast, the featural processing of non-experts was largely unaffected. The claim is then that faces are recognised by a domain-general mechanism for expert (i.e. configural) within-category subordinate discrimination.

Gauthier and colleagues (Gauthier, Tarr, Anderson, Skudlarski & Gore, 1999) argue that faces are special *only* as the most commonly encountered case of expert subordinate visual recognition. These authors have attempted to manipulate expertise by use of training studies (Gauthier & Tarr, 1997). For example, in one study participants were trained (over several days) to become expert at the subordinate classification of 'greebles'. These stimuli are computer-generated objects that share a common structure, belong to 'family' and 'gender' categories, and are recognised by name. After training, Gauthier et al. found that greeble recognition showed the hallmarks of expertise: it was as fast at the subordinate as at the basic level, and was disrupted by changes to configural information such as inversion. These effects were not found with novice participants. In other words, these authors show how considerable practice with non-face objects can lead to some effects previously considered to be face specific. However, these studies have been heavily criticised (Farah, 2000). Unfortunately, greebles tend to be perceived as very face-like, and may have been processed by the brain as such. Thus the question of domain specificity of recognition still remains uncertain.

1.3 Prosopagnosia

Prosopagnosia is caused by focal bilateral (and occasionally unilateral right hemisphere (RH)) brain damage that often includes lesion to the inferotemporal cortex in the region of the fusiform gyrus. It is a disorder in which the recognition of faces is seriously impaired relative to the recognition of objects. However, it is still unclear how specific the disorder is in relation to faces. This may be because

prosopagnosics are a heterogenous group. The exact nature of the recognition problem with faces is probably caused not only by the area of insult but also the state of the neural pathways (which are difficult to identify) between damaged and intact brain areas.

De Gelder and Rouw (de Gelder & Rouw, 2000b) make the distinction between those prospagnosics with 'positive' and those with 'negative' symptoms. Both groups are unable to recognise faces and present with similar behaviour at the clinical level. However, those with negative symptoms have lost face recognition and treat faces like any other kind of visual stimulus. In contrast, those with positive symptoms continue to treat faces differently to other stimuli, but this treatment actively impairs their recognition. For example, some cases have been reported in which the patient suffers an 'inverted inversion effect' (Farah, Wilson, Drain & Tanaka, 1995) in which they are more accurate at matching upside down than upright faces. It may be that these patients still have some vestigial functioning of damaged face mechanisms, since if the lesion had completely 'knocked out' a face module then the individual should be equally bad or good at applying their object recognition skills to faces regardless of orientation. Instead, these patients are good at matching inverted faces but suffer inhibition in processing upright faces (resulting in performance near to chance).

De Gelder and Rouw have tested whether inverted inversion effect patients suffer from an inability to overcome configural processing carried out by a damaged mechanism. In typical adults, as described in previous sections, face configuration can facilitate recognition of face features. In experimental tests, an isolated facial part can be matched more efficiently to the correct face presented upright than when it is presented inverted or scrambled. However, in the case of one classic prosopagnosic (LH), performance was at chance when the feature was shown in the context of the upright face. In contrast his performance was good when the face was inverted or scrambled. In other words his performance was abnormally inhibited as opposed to enhanced by the upright face context. It is not the case, then, that all

prosopagnosics use the featural processing of their 'preserved' object recognition mechanism to recognise faces. The interaction between damaged and intact areas appears to be critical.

Configural (upright face) interference effects in prosopagnosia highlight the importance of the featural / configural dissociation reported in the typical adult literature. It is further supported by other cases of 'object agnosia'. For example, patient CK lost feature based processing and as a result was unable to recognise common objects, although his face recognition remained intact (Moscovitch, Winocur & Behrmann, 1997). However, the difference between featural and configural processing is not the whole story. For a dual recognition system (mainly configural processing of faces versus mainly featural processing of objects) account to be valid, the inverted inversion effect in prosopagnosics must occur only for faces. This is not the case. The abnormal effect also carries over to processing of other objects, which may implicate a single recognition system that carries out all processing for all stimuli but carries out more configural processing for faces.

Acquired prosopagnosics are individuals who have expertise with faces that is then lost. The brain develops in the typical way and then has some of its processing mechanism removed. However, developmental prosopagnosics are individuals who never learn to recognise faces. These are very rare individuals who never develop expertise with faces and therefore (according to the featural / configural hypothesis) should not process faces configurally. In addition, these patients should show no normal inhibition or facilitation of recognition attributable to configuration encoding. The simplest test of this hypothesis is to use a face inversion task, on which there should be no difference between recognition of upright and inverted faces for these individuals. This is indeed what has been found with one developmental prosopagnosic individual (de Gelder & Rouw, 2000a). These results, and those described above from studies of acquired cases, are broadly consistent with the non-modular accounts of face processing: recognition depends on

experience with using a general mechanism for configural recognition (Damasio, 1990).

The most recent data from De Gelder and Rouw (de Gelder & Rouw, 2000b) offer some insight into the mechanisms involved in face processing. These authors tested two individuals, one with developmental and one with acquired prosopagnosia, on a face detection task. Stimulus presentation was either speeded (50 or 200ms) and followed by backward masking, or with unlimited viewing time. Both participants were at ceiling under speeded conditions for detecting the presence of a face. However, the performance of the individual with the acquired disorder dropped to chance when time was unlimited. This is in contrast to typical controls and the developmentally disordered individual who showed no decrement with length of stimulus exposure. Such results suggest that recognition abilities are activated with increased viewing, which then interfere with detection. It appears to be the inhibitory effect of a damaged system attempting to work that causes the detection decrement in acquired prosopagnosia.

At least one classically cited study (McNeil & Warrington, 1993) of the prosopagnosic patient, WJ, provides support for a dual mechanism detection and recognition hypothesis. After the stroke that caused the disorder, WJ became a sheep farmer. Despite being unable to recognise human faces, WJ was eventually able to individually identify his sheep. McNeill and Warrington compared his recognition of human faces and various kinds of sheep faces, to the recognition levels of controls on the same stimuli. They found for the control group that even those who worked with sheep were better at recognising human than sheep faces. In contrast, WJ performed very poorly with human faces and at expert levels with sheep faces (which he is presumed to have processed configurally). There are many possible explanations for this prosopagnosics performance. It is possible that the human face recognition 'module' had been specifically damaged. Alternatively it may suggest that prosopagnosia is not necessarily a deficit in recognition of individual exemplars of a homogenous category (the 'configural hypothesis), but that earlier processing,

for example by a face detection mechanism, can interfere exclusively with the processing of human faces. In contrast, these data may be used to suggest that human face encoding is carried out on the basis of configuration, for example in the form of distance from a prototype, but the human face prototype has been damaged.

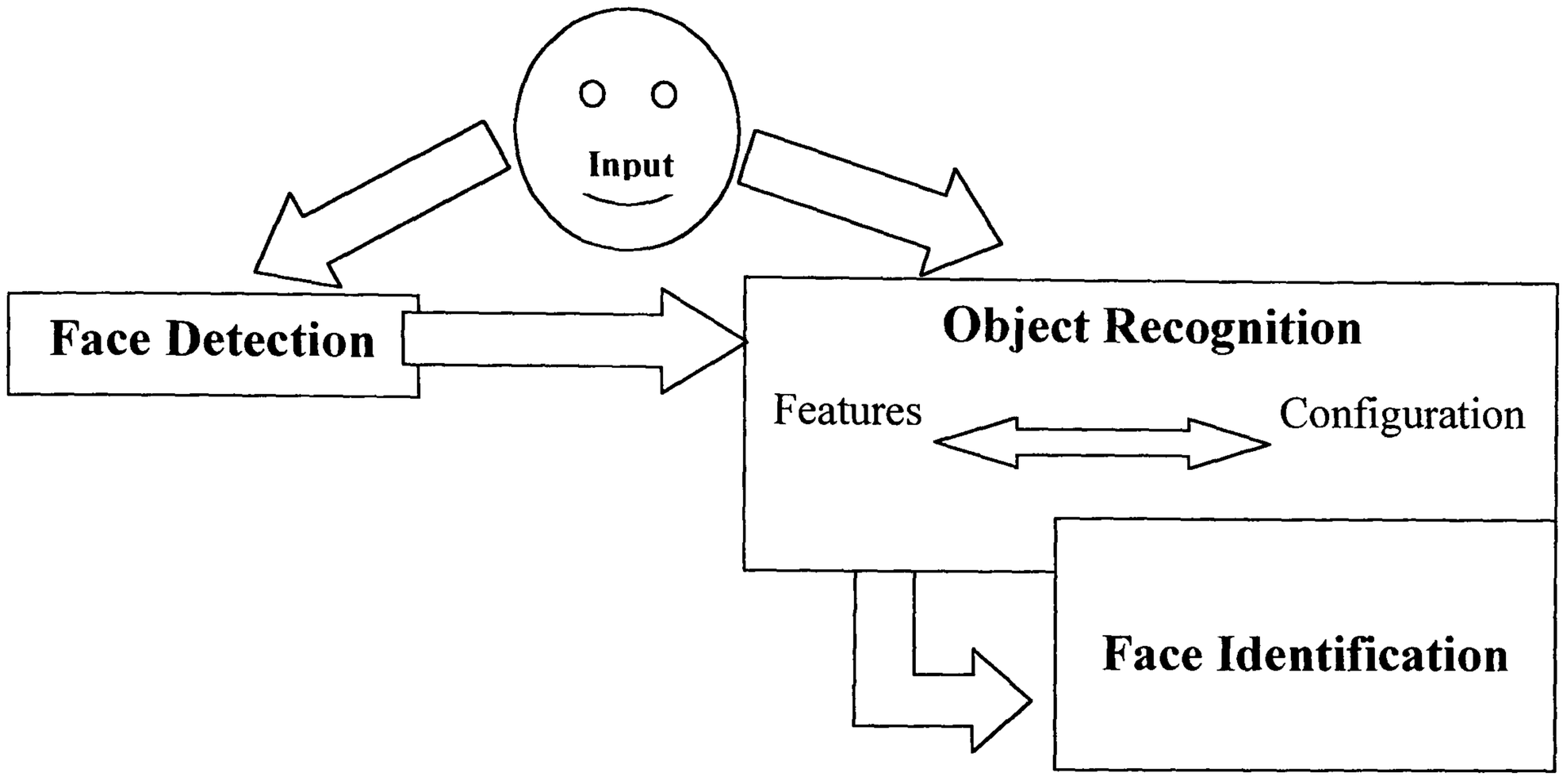


Figure 1.1 Dual Route model of Face Recognition (de Gelder & Rouw, 2000b)

Illustrated in figure 1.1 is a dual route model of face recognition proposed by de Gelder and Rouw (de Gelder & Rouw, 2000b) to account for the many findings of the prospagnosia literature. In this model, the ontogenetically primitive face detection system (based on something like the CONSPEC model, see infancy section of this chapter) is largely independent of face experience, but highly specialised for detecting the presence of a face stimulus. It is fast, requires only coarse representations, and is not sensitive to identity or any other aspect of the face like gender, familiarity etc. This system probably 'triggers' exogenous attention. In contrast, the face identification system is slow, shaped by experience, and shares at least some resources with the object recognition system. It requires finer representations and probably consists of many sub-processes and systems. According to de Gelder and Rouw, any part of the system can be knocked out, but some interactions will remain. For example, in the case of those with 'positive symptoms' of prosopagnosia, face detection remains intact. This mechanism sends

configural face input to the identification system, which overrules the feature based 'object processor', and stimulates a damaged face identification mechanism. This is the first model of prosopagnosia to explicitly attempt to tackle development and the role of experience (although there have been many other 'static' models (Damasio, Tranel & Damasio, 1990; Farah, 1990; De Renzi & di Pellegrino, 1998)).

The most important feature of the 'dual route model' to the current discussion is that there is a functional and anatomical distinction between detection and recognition mechanisms, or 'early' and 'late' processing. This could be analogous to the distinction illustrated in the previous section between early 'encoding' of configuration, and later 'recognition'. The intricacies of the model will not be debated here, but evidence to support the configural detection / encoding and recognition distinction will be discussed in the following sections, considering infancy, childhood and ERP research.

1.4 Development

Investigations of the typical adult are limited in the sense that they can provide information about eventual domain specificity and spatial localisation, but can say little about how the system reached this endstate. Instead, research on different points in the developmental span (in conjunction with research into abnormally developing systems like developmental prosopagnosia) has been used. In this section, typical development is considered from the newborn baby up to infancy. This work is important for three reasons: first to illustrate the importance of development as opposed to maturation, second to support the distinction between detection (which involves the encoding of a prototypical configuration) and recognition, third to highlight the contribution that WS research could make to these discussions.

1.4.1 The Newborn

One of the first sights for a baby following birth is the human face, and even at such an early stage babies show an interest in faces and face-like patterns, (Morton &

Johnson, 1991, Simion, 1998 #3166). It is thought that face processing at this young age is mediated by subcortical mechanisms. The function of such mechanisms is of particular interest because of the lack of visual experience. This means that any innate representational bias that may affect the subsequent development of the system can be investigated.

All that is required to elicit an orienting 'face detection' response from newborn is a schematic version of a face, with three blobs for eyes and mouth in a triangular arrangement (Morton & Johnson, 1991). The question is whether this is due to an innate preference for face-like patterns or because these patterns have other qualities that the infant is attracted to over the control stimuli. Work from Farroni and colleagues (Farroni, Valenza, Simion & Umilta, 2000) indicates that it is because typical newborns have a preference for top heavy stimuli that contain most energy in the upper half of the visual field. In other words, when presented with an upright or inverted 'T' shape, infants prefer to look at the upright one. This is general to non-face stimuli but may be considered to be a coarse innate bias to face-like configurations. Such a bias may have its evolutionary origins in the adaptive advantage of newborns orienting to the faces of the adults on whom they depend.

Morton and Johnson (Morton & Johnson, 1991) were the first to propose the existence of an innate 'face-like representation' in the newborn. They suggest that the preference for face-like stimuli is due to an innate subcortical mechanism called 'Conspec' that causes an orienting response to stimuli matching a skeletal three dot representation (i.e. faces). Conspec is considered to be an 'attractor' device, which ensures face input to the developing system. The weight of evidence does indicate that newborns prefer even the most basic of face-like patterns over other patterns. Moreover, there is increasing support for the view that this preference is subcortically mediated. For example, subcortical systems are known to be sensitive to stimuli that are moving, or are in the peripheral but not central visual field. Young infants in turn only preferentially orient to moving faces or faces presented in the peripheral field (Simion et al., 1995). The face is probably unique in being the only

visual stimulus innately represented (no matter how sparsely) at the subcortical level.

Newborns do not just orient to faces, they are also able to distinguish between them. A baby of only a few hours old will look longer at the mother's over a stranger's face even when other cues like smell are eliminated (Bushnell, Sai & Mullin, 1989). Unfortunately, the visual perception of a newborn is limited by poor acuity which means that processing style is difficult to ascertain. There is some evidence though that discrimination is based on hairline and contour more than on internal facial features. In infant studies recognition is indexed by a longer look to the familiar stimulus. In such a study on newborns, looking time was longer only when a full face and not just the internal features were presented (Pascalis, de Schonen, Morton, Fabre-Grenet & Deruelle, 1995). Eye scanning studies corroborate this finding, and have shown that newborns tend to scan the outside of any shape, including faces, rather than the internal elements (Maurer, 1983). This indicates that all visual stimuli are recognised on the basis of the external whole rather than the features.

1.4.2 The Infant

The face processing of the infant at 6-8 weeks undergoes a behavioural shift that is thought to index the transition from subcortical to cortical processing. As already described, newborns show preferences only to moving stimuli, or those in the peripheral visual field. However, at 6 weeks of age preferential tracking of faces declines, and is followed in the subsequent 6 weeks by preferences in the central visual field for normal faces and face configurations as opposed to those with contrast reversed or features scrambled. Nasal / temporal hemifield assymmetries disappear (Johnson, Dziurawiec, Ellis & Morton, 1991). For example, newborns orient more frequently to stimuli in the temporal hemifield, and this is thought to be because the temporal hemifield directs more information to the subcortical (retinotectal) pathway. In contrast, older infants show no hemifield differences, which is thought to be due to the maturation of the cortical (geniculostriate) pathway. By 8 weeks of age infants become more sensitive to the internal features of

the face (Pascalis et al., 1995), and can recognise a familiar face from a novel viewpoint by internal features alone. Scanning studies confirm that there is an increase in the visual scanning of these areas (Maurer, 1983). This suggests that the face processing of the 2-3 month old infant is becoming more adult-like, and may set the stage for the adult strategy of encoding configuration.

The processing of faces, and particularly configural face information has been found to be more right hemisphere (RH) than left hemisphere (LH) lateralised in adults (see below and section on ERPs). At 16 weeks of age, hemispheric differences in processing are evident in infants. The primary visual cortex in the RH receives neural projections from the left visual field (LVF) and vice versa. Adults normally show a right hemisphere (LVF) advantage (faster reaction time and smaller errors) for face recognition. De Schonen and colleagues have demonstrated that 4-9 month olds exhibit a shorter latency for eye movements to the mother's face compared to a stranger's face only if presentation is to the LVF rather than the RVF (de Schonen & Mathivet, 1990). The opposite is true of simple geometrical shapes, which are discriminated better in the RVF. Further, these researchers have shown that these hemispheric differences are correlated with different encoding. The right hemisphere is better at detecting differences in the configuration of patterns, and the left is better at detecting feature changes.

1.4.3 The Role of Experience in Infant Face Processing

The progressive changes in face processing over the course of early infancy have been outlined. However, this development can be explained by attributing more or less of a role to visual experience. There are five main hypotheses (De Haan & Halit, 2000): Experience-Independent, Experience-Dependent, and three formulations of the Experience-Expectant hypothesis.

Experience-Independent

This is the strongest application of Fodorian modularity to explain changes in face processing over chronological age. According to the proponents of this hypothesis,

face recognition is achieved by the functioning of a single, innate and cortically-specified, domain-specific module. Visual experience is considered irrelevant (except as a trigger) to the development of the mechanism, which does not change so much as unfold according to a prespecified schedule. The behavioural changes that have been documented in the literature are attributed to the maturation of the module, increases in processing speed, and generally higher quality visual inputs with age. None of the literature reviewed so far would support such an approach, first, because there is evidence that face recognition is achieved by the functioning of far more than one system, and second because there is no evidence to support innate cortical specification. The processing model proposed by De Gelder and Rouw (see Figure 1.1) does make some claim for an innate face-specific 'detection' mechanism. However, the infancy research reviewed above suggests that such processing stems from an innate subcortical bias, and it is an interaction of this factor with experience that determines cortical processing.

One obvious way of testing the Fodorian hypothesis is to investigate the face processing system of individuals initially deprived of visual experience and who are then exposed to faces. This has been achieved by studying infants treated for congenital bilateral cataracts at six weeks of age (Maurer, Lewis & Brent, 1989). Results showed that, in contrast to the strongest predictions of the experience-independent hypothesis, the infants behaved like newborns. So experience must be important at the very least for triggering the development of the face processing system. A recently published longitudinal study has also shown that the face processing of such individuals does not 'catch up' but actually develops atypically (Le Grand, Mondloch, Maurer & Brent, 2001). This supports an experience expectant and not a maturational view of face processing development.

An alternative method of looking for confirmation of an innate face processing module is to look for a double dissociation with object processing, across developmental disorders and individuals with congenital brain damage. For example, people with Williams Syndrome have been claimed to show a dissociation

between 'intact' face processing and severely impaired object processing (see Chapter Two). Initially this research could be used as evidence in support of the modularity hypothesis. However, recent data suggests that the face recognition of people with WS is far from intact and is achieved by atypical strategies. However, the state of the detection / encoding stage, which satisfies more of the modularity criterion than recognition, has not been investigated. Thus the debate is still open. It is possible that WS could be used in support of both arguments: the innate basis of the domain-specific configural detection and encoding mechanism, and the domain generality (or progressive face specialisation) of the recognition system. This is the topic of the current thesis and will be discussed in depth in the next chapters.

Experience Dependent

At the opposite end of the theoretical spectrum lies the view that visual experience plays the essential role in the 'modularisation' of face processing (Diamond & Carey, 1986). This is a hypothesis in which the requirement for subordinate category individuation prompts the specialisation of a face processing mechanism. It also states that extensive experience with the subordinate classification of other non-face stimuli could potentially prompt a similar process of specialisation. Unlike an 'experience expectant' view (see below), this hypothesis implies that age or stage of development is relatively unimportant, because the cortex is equally 'ready' to change in response to input throughout development.

Like the Fodorian hypothesis, the experience-dependent hypothesis would predict that infants born without vision who were then treated (e.g. for congenital bilateral cataracts) would follow the same developmental pathway as controls but with a slight delay equal to the age of the child at treatment. As already mentioned, this has not been found to be the case (Le Grand et al., 2001).However, the two hypotheses do differ in their view of the effects of expertise with non-face stimuli. The Fodorian view would not predict neural specialisation on the basis of expertise. Yet, as already mentioned, in training experiments with nonsense objects like greebles (Gauthier & Tarr, 1997), and an experiment with 'natural experts' (dog judges)

(Diamond & Carey, 1986), specialisation does appear to occur. This cannot be explained by the experience-independent approach except by questioning the validity of the experimental paradigm or imaging measures. Alternatively, it could be claimed that the face processing system is in some way 'poached' due to the unusual requirements of the other stimuli with which the individual is expert (although, 'poaching' also sits very uneasily with the domain specificity requirement of a Fodorian framework). In contrast, the experience-dependent hypothesis would predict specialisation. However, it would not be able to explain the increasing evidence for subcortical bias for face stimuli in the infant, (or a face-specific detection mechanism) except by assuming that they reflect more general constraints in infant visual preferences. However, it would be unable to explain why these early 'general' preferences would exist to bias the system to prefer stimuli which share the characteristics of faces.

Experience Expectant

There are three versions of the experience expectant hypothesis (De Haan et al., 1999) which lie in between the extreme views already outlined. These three views all have in common the requirement that face experience be achieved within certain time windows to guarantee the normal development of the face processing system. The broad idea is that there is some expectancy of the system at the neural level for a 'species typical experience' but only for a limited time. If initial experience falls outside of this time window, then development may progress atypically. The structure of the environment (patterns of light and dark, faces of con-specifics), in interaction with a very minimum specification at the genetic level, then regulates face processing development.

Conspec/Conlearn

The concept of Conspec (Morton & Johnson, 1991) was described above. It is a simple attractor mechanism that stimulates orienting to face-like patterns. One of the purposes of this purported subcortical mechanism is to provide 'face biased' input early on in the development of the cortical visual processing system. In effect this ensures specialisation for faces because they are the dominant visual input to the

cortex. The subcortical face bias is then sublimated by the cortex when the foundations for face specialisation have been laid. In addition cortical 'Conlearn' allows the learning of individual exemplars of faces. This hypothesis explains the early preference of infants for faces over other patterns. It also allows the generation of specific predictions about possible developmental abnormalities. If faces are not the dominant input to the cortical visual system in the early stages of development, then specialisation may fail to occur (developmental prosopagnosia). Alternatively, if subcortical Conspec is not overidden by cortical development at the 2 month transition stage, then the mechanism may continue to cause face orienting and potentially inhibit the processing of other stimuli (this is one, as yet untested, hypothesis to explain the purported 'over specialisation' for face processing in Williams Syndrome).

Perceptual Narrowing

Nelson (1995) argues that the specialisation of the cortex for face processing may be analogous to the specialisation for speech perception. Infants are initially able to discriminate a wide band of speech sounds, but this ability narrows with experience until 12 months of age, when only the native language contrasts can be behaviourally discriminated (although see Rivera-Gaxiola (Rivera-Gaxiola, Csibra, Johnson & Karmiloff-Smith, 2000) for electrophysiological evidence). With face processing it may be that the possible human face recognition cues are part of a larger class of stimuli e.g. visual objects or faces including animal faces. With experience this may become narrowed to include only human faces, and then further narrowed to include only cues that are relevant to specific aspects of face processing (e.g. identity vs emotion). There is some evidence in support of this view. For example, ERP evidence suggests that human faces and monkey faces evoke the same processing in the 6 month old, whereas a typical adult processes these faces differently (de Haan et al., 1998). In addition, monkey faces appear to be better discriminated by 9-month olds than by adults (Nelson, 1993). Both of these results suggests that the wide category 'face' containing all faces, becomes narrowed by experience to discriminate the faces of conspecifics. This view may be considered to

be a description of the development of the 'Conlearn' component of the previous hypothesis.

Rates of Development

De Schonen and colleagues (de Schonen, Gil de Diaz & Mathivet, 1986; de Schonen & Mathivet, 1989; de Schonen, Deruelle, Mancini & Pascalis, 1993) attempt to provide a developmental account for specific aspects of the adult face processing system: the right hemisphere advantage and the configural processing bias. These are not explictly tackled by the other experience-expectant hypotheses. De Schonen and colleagues argue that these characteristics exist as a consequence of several factors: newborns preferentially attend to faces; they receive visual information mainly by the low spatial frequency channels; and the right hemisphere generally develops ahead of the left hemisphere. This results in the right hemisphere (RH) becoming specialised for processing faces configurally, because only configurations can be differentiated between faces on the basis of low spatial frequencies. By the time the relevant parts of the left hemisphere (LH) have become functionally mature (by 2 months old), infants may be able to process high spatial frequencies. This means that the LH can begin by processing a wider range of frequencies than the RH did when it started processing visual information. The LH may therefore perform different kinds of processing to the RH.

There are two lines of evidence to support de Schonen's hypothesis. First, visual field experiments suggest that from four months of age, infants shift gaze to the face of the mother over a stranger if both are presented in the left visual field (LVF) (approx 95% of projections arriving in RH only). Presentation to the right visual field (RVF) does not cause a preference. This is in contrast to the processing of geometric patterns, which are discriminated equally well in either field. The second line of evidence is that one infant (Nc) ERP is larger for a familiar face (the mother) compared to that of a stranger for the right and mid-line but not the left anterior temporal electrodes. In combination, both studies support the hypothesis that there is

a right hemisphere advantage for face processing by 4-9 months of age, although this RH advantage may carry over to other global visual patterns as well as faces.

Summary of Infant Development

Face detection by neonates is aided by a coarse subcortical bias to look at top-heavy patterns. This ensures face input to the developing system. It may also set up the cortical bias in the RH to detect and encode faces by configuration. Experience is essential to the development of both face detection and recognition. In addition there is evidence to suggest that the input of experience is, at least to some extent, time sensitive

1.4.4 Childhood to Adolescence

Infants show an impressive range of face processing abilities, yet the course to adult-like recognition is still unclear. It is known that the face encoding and recognition in children between the ages of 2 and 10 years undergoes significant improvement from extremely poor to near adult levels (see below), but there is some controversy about what drives this change. For example, the inversion effect has been found to increase in size with age (Diamond & Carey, 1977). For some time it was argued from these data that face processing shifted from analytic to configural processing over development with increasing expertise . However, this has recently been called into question because the effect of orientation in the younger groups may have been masked by floor effects. In response, Carey (Carey, 1992) tested 6-7, and 10 year old children, and adults, on the Young et al. task (Young et al., 1987) described previously this chapter, in order to investigate the encoding of configuration in a different way. In this study the reaction time of all groups was increased to the merged mismatch face when presented upright but not inverted. This indicates that there is some configural processing of upright faces. However, the older groups were more affected by inversion than were the younger group, suggesting that inverted faces of this type were encoded less efficiently (more configurally) with increasing age. In another study designed as an alternative to an inversion experiment, Tanaka et al. (Tanaka, Kay, Grinell, Stansfield & Szechter, 1998) report that children

between 6 and 10 show the typical recognition advantage for facial parts presented in the face context rather than in isolation, suggesting again that configuration is encoded by children. In contrast, Schwarzer (Schwarzer, 2000) claims that children process all visual stimuli, including faces, analytically. Children and adults were compared in the strategies they used to categorise faces which varied in different attributes (eyes, nose, mouth, outline). The results showed that adults based their categories on the whole face, using most of the attributes together, but the children used just single facial features. In addition, when faces were inverted, adults switched to processing analytically whereas for seven year olds there was no effect of inversion on mode of processing.

A recent study attempted to test the inversion effect systematically by investigating performance on a picture-book task (Brace, Hole, Kemp, Pike, Van Duuren et al., 2001). The experiment was designed to eliminate floor and ceiling effects, to use a higher number of targets and distractors (more trials), and to keep the participants engaged with the task. In addition, the authors tested 153 children across the developmental span from 2 to 12 years. Most previous studies have concentrated on children between 6 and 10 years because this was the period originally claimed (Carey & Diamond, 1977) to contain the qualitative shift in processing. However, Brace and colleagues argue for sampling from the whole developmental span in order to see the trajectory of change. Their results support this view. Not only was there a linear relationship between time taken to identify a face and age, but there was a significant interaction of stimulus orientation with age. Children of 2-4 years of age were faster to recognise inverted than upright faces, (an 'inverted inversion' effect), but all children from 6 years upwards showed the classic inversion effect.

There are several possible explanations for the apparent discrepancy between results on different experiments. As pointed out by Brace et al. (Brace et al., 2001), it is possible that the encoding switch is just much earlier than previously thought (i.e. at around 4 rather than 10 years). Very young children may attempt to use configural information to encode upright faces but do so inefficiently. A different explanation

is that changing strategies may be used on different tasks and over development, because processing *preference* changes over time. It may be incorrect to frame results in terms of *ability* because all age groups have the full range of strategies available. Alternatively, results can be explained by positing the increasing development of a face detection mechanism that encodes on the basis of configuration. This is the mechanism that shapes the progressive specialisation of the face recognition system. However, in very young children it may inhibit the processing of upright faces by suppressing analytic processing. The mechanism detects an upright face on the basis of configuration and sends low quality information to an inexpert recognition system. A feedback loop stimulates progressive specialisation of both systems. In other words, it is configural encoding of a pre-recognition system, and the resulting progressive specialisation of the recognition system, that develops with age and experience.

Summary of Face Processing Development through Childhood

In summary, most studies offer some evidence for an increasing reliance on configural processing over development. This may not take the form of a 'shift' in strategy but a gradual increase in expertise due to increasing cortical specialisation.

1.5 Electrophysiology

1.5.1 Intra-cranial ERPs

A complement to cognitive studies is to take a measure of brain activity and its changes over time, in relation to different stimuli. Event-related potentials (ERPs – see Chapter Three for description of technique) are one such measure that can been used to explore face processing. Waveform components of event-related electrical activity recorded directly from the cortical surface have been described by in a series of papers by Allison and colleagues (Puce, Allison, Asgari, Gore & McCarthy, 1996; Allison, Puce, Spencer & McCarthy, 1999; McCarthy, Puce, Belger & Allison, 1999; Puce, Allison & McCarthy, 1999). Their research can help answer questions

about both temporal processing (which can be used to answer questions of domain specificity) and spatial localisation. These authors presented epileptic patients, during monitoring for seizures, with faces and other comparison stimuli. To keep them alert, their task was to press a button in response to a specified target e.g. butterflies. One goal was to identify early face-specific potentials that were a priori defined as components that were at least twice as large to faces as to any other stimulus category. The N200, recorded from ventral occipito-temporal cortex, the fusiform and the middle temporal gyrus (75 sites in total), was most consistently found to satisfy this face-specific criterion (compared to cars, scrambled cars, letter strings, butterflies, flowers, and scrambled flowers). In addition, when these regions were stimulated, patients either became unable to identify familiar faces or suffered face hallucinations.

The location and response properties of the N200 have been mapped out (McCarthy et al., 1999). The component is found bi-laterally to upright faces, but to inverted faces shows a RH decrease in amplitude and an increase in latency. This is not the case for other stimuli, like cars, which were found to evoke the same response regardless of orientation. On the basis of this face-specific inversion effect and the fact that the N200 is temporally the first reliable sign of 'face-specific processing' the authors propose that it reflects 'activity related to the structural encoding stage'. In other words, the N200 is thought to reflect the stage at which face detection is carried out on the basis of configural information.

The relationship of the N200 to structural encoding was tested by response to familiar versus unfamiliar faces. At the encoding stage, familiarity should not affect the amplitude or latency of the component. This hypothesis was supported as no effects were found (McCarthy et al., 1999). It was further supported by evidence that the N200 remained unaffected by learning of faces and gender discrimination. The only manipulations that did increase the amplitude of the component were blurring the faces, increasing their size or averting the eyes, suggesting an increase in effortful encoding. Parts of the face that are usually less examined like noses and

lips, increased N200 latency when presented in isolation. This increase in response time was interpreted as reflecting a delay in processing due to the increased difficulty in detecting as 'face'. Non-face stimuli elicited a component that was, on average, only 16% of the size of that to a face.

Intra-cranial ERP results have been argued to make a strong case for describing face perception as modular (McCarthy et al., 1999). The N200 is generated by a population of neurons that 'responds to a preferred input in an automatic, mandatory fashion and carries out specific computations that are immune to outside influence'. However, this conclusion may be premature. A caveat to the McCarthy conclusion must be that (as the authors admit) their results say nothing of genetic specification or development of the face perception process over time. Thus it is unknown whether the N200 reflects processing that fulfills all of Fodor's criteria for modularity. In addition, the results do provide supportive evidence for the localisation of one process, which is presumed necessary for face detection, but the preferential activation may be due to the lack of adequate control stimuli. As described above, faces appear to be detected on the basis of configuration because they are such a homogenous class and require precise individuation. So the N200 may not reflect face-specific processing per se, but detection on the basis of configuration.

The question of the organisation of the ventral temporal cortex is subject to much debate in all localisation studies. Is the brain arranged according to the processing it carries out, or it is arranged according to the information being processed? An alternative technique has been used in an to attempt to find out. Functional Magnetic Resonance Imaging (fMRI) is a technique for determining which parts of the brain are involved when a participant is engaged in particular kinds of cognitive processing. It works on the assumption that activity of a brain area in response to a stimulus will result in increased blood flow to that area. The method has highlighted an area of middle fusiform gyrus in the posterior temporal lobe (the 'fusiform face area' or FFA), that consistently shows greater activation during face perception tasks

than during tasks that involve the perception of other objects (scrambled faces, consonant strings, or textures) (Kanwisher, McDermott & Chun, 1997).

Gauthier et al. (Gauthier et al., 1999), using the strongest form of the expertise hypothesis, predicted that the FFA could be shown to be active, but not selective, for face encoding. That is, the activation in the FFA should depend on the level of the participants expertise with a given object category. As mentioned in a previous section of this chapter, this author and her colleagues trained participants to categorise novel objects called 'greebles' until they were experts. Before the training started the participants were imaged, and they were repeatedly imaged throughout training. At the beginning of training there was significantly higher activation of the bilateral face regions to upright faces than to upright greebles, especially in the RH. As expertise increased, however, the RH preference for faces over greebles decreased until there was no significant difference.

The behavioural and brain imaging results for greeble recognition have lead Gauthier (Gauthier et al., 1999; Gauthier, Tarr, Moylan, Skudlarski, Gore et al., 2000) to claim that the FFA is not face specific but can be activated by objects given an interaction of two conditions: (1) the level of categorisation of the object allows subordinate recognition of the individual e.g. John versus Bob; and (2) experience with identifying the objects leads to expertise which results in configural processing. They claim that the strongest interpretation of their results ' is that the face-selective area in the middle fusiform gyrus may be most appropriately described as a general substrate for subordinate-level discrimination that can be fine-tuned by experience with any object category.' (Gauthier et al., 1999. pp 572).

As mentioned in the section on behavioural studies, the most significant criticism of Gauthier's work is that exemplars of the object category used bear more than a passing resemblance to faces. It is possible that her findings will not generalise to all object categories, but only ones that look face-like to some degree e.g. in having eye and nose like protrusions, being of constant colour, and having a smooth organic

surface. To counter this criticism, Gauthier has shown that for car and bird experts, there is more activity of the FFA to the 'expert' compared to the 'novice' stimuli (Gauthier et al., 2000). Car experts show activation in the FFA to cars but not to birds, and vice versa. However, it should be noted that despite these changes in activation there is always more activity in the FFA for faces. This may be because the amount of expertise with faces is always higher than for any other kind of stimulus. Alternatively, as Kanwisher suggests (Kanwisher, 2000), the FFA may be a specialised module for face encoding which is only optimally active when a face is present but can be 'used' for other stimulus processing when necessary. At present, it is unclear how this debate can ever be answered decisively using the fMRI technique. It allows the researcher to see which part of the brain is active but not the time course of activation, or the correlation in time with other brain areas. It may be research on the interaction of activity of different areas over time or cortical specialisation over development (for example of adults with experience from early childhood of subordinate categorisation with stimuli such as dogs) that eventually forces some conclusion to this debate.

1.5.2 Scalp-recorded ERPs

The ERP method has been used to attempt to find face-specific brain activity and to identify changes in activity, and co-activity, over time. To date two possible 'face specific' candidate components have been identified: the Vertex Positive Potential (VPP), largest over Cz (Jeffreys & Tukmachi, 1992) and the N170, largest over occipito-temporal sites (Bentin, Allison, Puce, Perez & McCarthy, 1996). Both peak at about the same time after stimulus presentation and are for the most part similarly affected by experimental manipulations. For this reason it is unclear whether one reflects the opposite di-pole of the other, or whether they reflect different processes (see (Rossion, Campanella, Gomez, Delinte, Debatisse et al., 1999; Taylor, Itier, Allison & Edmonds, 2001)). The VPP is slightly less sensitive to faces than the N170 (Rossion, Campanella et al., 1999), may only emerge late in adolescence (Taylor, Itier et al., 2001) and is over areas less likely to be directly involved in early visual processing (although the brain is a volume conductor so there is no direct

relationship between scalp sites and neural generators). For these reasons, most recent research, and that presented here, has been conducted to observe the N170 response alone.

The N170 is a negative deflection in the lateral posterior-temporal waveform (T5 / T6) that peaks between 120 and 200ms after stimulus onset. It can be observed to a range of visual stimuli but is usually largest in amplitude to faces. The component was first noted in a study by Botzel (Botzel & Grusser, 1989) but was systematically described by Bentin and colleagues (Bentin et al., 1996). These authors presented participants with a randomised order of stimuli from different categories: faces, scrambled faces, cars, scrambled cars, and butterflies. The task was to count the number of butterfly presentations. Fourteen electrodes were used in standard sites, and the waveforms from the different categories compared. It was found that faces elicited an N170 distributed focally over the lateral posterior scalp (electrodes T5 and T6), with a non-significant trend to RH lateralisation. None of the stimuli other than faces elicited an N170 according to these authors. However, it should be noted that there was a N170 equivalent negative deflection in the waveform, occuring at around the same time, that was positive rather than negative in amplitude. Absolute amplitude of the component is essential to support the claim that the N170 is only elicited to faces. Components are usually named according to the direction of deflection rather than the absolute amplitude (which could vary according to low level stimulus features like luminance or contrast), in which case the N170 *was* evoked by other stimuli but remained much smaller in amplitude than to faces.

In following studies, Bentin et al. (Bentin et al., 1996) attempted to test the specificity of the N170, by comparing activation to faces with activation to hands, animal faces and furniture. The results suggest that the N170 is sensitive not to faces in general or even human body parts, but to human faces and face parts specifically. When orientation sensitivity was tested, the N170 to faces was significantly larger in the RH and 10ms later in both hemispheres with inversion. Cars were not affected by orientation, supporting hypotheses that inversion changes the processing of faces

but not other stimuli, even those to which an individual is frequently exposed. Taken together these results suggest that the N170 is sensitive to changes in configuration. To test this hypothesis, the authors presented participants with different isolated features of faces, and compared the N170 to that obtained for whole face activation. It was found that increasing the disembedding of the eyes from its context in a normal face increasingly affected the amplitude of the N170, whereas other isolated face parts did not differ from each other or produce an N170. Bentin et al. conclude that the N170 is not just sensitive to configural changes but reflects the activity of a specialised eye processor.

In summary, Bentin and colleagues examined the characteristics of the N170 and found:

- It is only evoked to human faces and face parts,
- It is most sensitive to human eyes,
- It is sensitive to changes in face configuration,
- It is larger and later to inverted faces,
- It is not evoked (much smaller) to objects or non-primate animal faces,
- It is not sensitive to the inversion of objects,
- It is larger on the RH to faces,
- Data are consistent with a neural generator in the occipito-temporal sulcus, lateral to the fusiform / inferior temporal region that generates N200.

Much work has taken place since these results were published. A number of researchers have attempted to further delineate the specificity, sensitivity, laterality and developmental trajectory of the N170 to faces. The specificity of the N170 to faces, with increased amplitude, compared to other stimuli has been well replicated (see (Rossion, Gauthier, Tarr, Despland, Bruyer et al., 2000). However, this is an inadequate base from which to claim specificity of processing, since there is sometimes a comparable difference in amplitude between other object categories. In order to make the strongest specificity claim, it should be shown not only that faces are processed differently to other objects, but that there are no significant differences

between objects. That is, other visual objects are processed by way of a general object recognition mechanism. This appears not to be the case, since houses may evoke a component which is bigger than that to shoes, butterflies and so on (Bentin et al., 1996). This could be due to low-level differences between stimuli, as could the difference between objects and faces. Alternatively, level of expertise with the stimulus class may be the significant factor. Expertise is a well-documented confound to the results of face processing studies and is discussed later in this chapter.

The characteristic of the N170 that does appear to be specific to faces is its tendency to increase in amplitude and latency with inversion. The component has not yet been shown to be sensitive in the same way to the inversion of any other stimuli. For example, Rossion et al. (Rossion et al., 2000) compared the effect on the N170 of inverting Greebles, cars, chairs, houses and shoes. No increase in amplitude with latency was found for any of these object classes (though an increase in amplitude with 'house inversion' in the absence of a latency effect has been documented, (Eimer, 2000)). This suggests that it is the decrease in configural information that causes the face specific effect.

Eimer (Eimer, 2000) has investigated the cause of the face inversion effect, by testing its response to face familiarity and differing attentional demands. Participants were presented with photographs of upright and inverted, familiar and unfamiliar faces and houses. Their task was to button press to either the presentation of a different stimulus category (hands), or to the repetition of a previously shown stimulus, or to digits superimposed in strings onto the stimuli. Results showed no effect of familiarity on the N170, and no change in the inversion effect for familiar versus unfamiliar faces, suggesting that the component reflects pre-identification processing. Likewise, differences in attentional demands made no difference to the amplitude of the face inversion effect.

Previous studies have suggested that the increase in amplitude to face inversion is due to an 'attentional processing negativity' associated with attention and task difficulty (George, Evans, Fiori, Davidoff & Renault, 1996; Rossion, Delvenne, Debatisse, Goffaux, Bruyer et al., 1999). This hypothesis would predict that actively directing attention towards the face (e.g. when detecting stimulus repetition) or away from the face (e.g. when detecting a digit) should modulate the inverted face amplitude. In contrast, attentional demands were found by Eimer (Eimer, 2000) to affect latency alone; the diversion of attention from the face caused an increase in peak latency for both inverted and upright stimuli. As a result, this author suggests that the timing of the N170 can be affected by attention directed away from the configurational analysis of faces e.g. towards another task. An alternative explanation for the face modulation of the N170 by face inversion is that an increased number of brain areas are involved in processing the inverted face. Studies using fMRI have found that inverted faces recruit not only 'face areas' like upright faces, but also surrounding areas that are involved in object processing (Kanwisher, Tong & Nakayama, 1998). The N170 inversion effect may then be a consequence of more widespread cortical activation (Rossion, Delvenne et al., 1999).

The relationship between structural analysis and the latency of the N170 is supported by studies in which face configuration is changed (Bentin et al., 1996), or attention is directed towards individual components of the face. For example, in a different study (Eimer, 1998), which also refutes the hypothesis that the N170 reflects the activity of a 'specialised eye processor', Eimer removed the eyes from the face stimulus and found an increase in peak latency compared to the original (eyes intact) face stimulus. To date all studies have now shown that an increase in the difficulty of configural processing corresponds with an increase in latency e.g (Bentin et al., 1996; Eimer, 1998; Bentin & McCarthy, 1999). One possible hypothesis is that individual features evoke a larger and later component, because they induce processing by a detection / encoding system which attempts to extract configural information and takes increased time to encode such atypical exemplars. One theory of how configuration is encoded is by reference to another prototypical

representation (Carey, 1992). The further from the prototype the face is (the more atypical, or less average) the longer it will take it to detect as a face, and the longer it will take to allocate to a position in the 'face space' in memory (Tanaka, Giles, Kremen & Simon, 1998). Alternatively it may be that eyes alone engage top-down processing mechanisms which attempt to complete the face (thus increasing latency) before allocating it a position in memory. However, these particular experiments are limited in not being able to shed light on the effects of expertise. As mentioned in previous sections, most people are highly expert at differentiating human faces, since they have to do it constantly in daily life. This is not the case for most other classes of visual stimulus. It is possible that the apparently face-specific effects are actually non-face specific configuration effects which only develop as a result of extensive subordinate category individuation.

A recent study attempted to demonstrate the effects of expertise on the N170 (Tanaka & Curran, 2001). In this experiment, the amplitudes of the N170 evoked to dog and bird stimuli were compared, for 15 bird and 15 dog experts engaged in a categorisation task. Results showed a significantly larger N170 to the 'expert' category stimuli than to the novice for each group. The N170 was over approximately the same scalp areas, and at roughly the same time as that found to faces in other studies. Unfortunately, however, conclusions from this study are limited by the lack of both face stimuli and a test of stimulus inversion. It is possible that the N170 to the expert category was still significantly smaller than that to faces in the same individuals. In addition, the study would have given much stronger support to the expertise hypothesis had the inversion effect been tested. This hypothesis specifically predicts that an inversion effect in amplitude and latency should be found for the expert and not the novice category. This prediction remains untested. As a consequence, it is clear that expertise can make a small difference to the amplitude of the N170, but the relationship between the N170 to faces and expertise effects is still unclear.

An alternative method of testing the specificity of the N170 component is to investigate those with abnormal face processing. Individuals with Williams Syndrome and those with autism will be discussed at length as the topic of the present thesis. However, cases of developmental and of acquired prosopagnosia have already been investigated. Eimer and McCarthy (Eimer & McCarthy, 1999) report ERP results to upright and inverted faces, and houses, for one such individual. Patient 'PHD' had suffered a head injury leading to severe prosopagnosia at the age of 19, and is reported to be impaired at both the structural encoding and the recognition stages of faces processing. Standardised measures such as the Benton test of face recognition revealed scores at chance. PHD's behavioural performance during the experiment revealed an impaired ability to detect the immediate repetition of unfamiliar face stimuli, even after an inter-stimulus interval of just 1300ms. The associated ERP results revealed an N170 that was undifferentiated for faces compared to houses (unlike typical controls who all showed a larger N170 to faces). Moreover, they revealed that the component was unaffected by face inversion. This is a highly atypical result that supports the relationship between the N170 and the structural encoding of faces. The authors conclude: 'ERPs may thus be used as markers for the selective impairment of component processes involved in face perception and identification' (Eimer & McCarthy, 1999, pp 259).

The case of PHD provides important convergent evidence to support the relationship between structural encoding and the N170 component. However, his deficit was acquired after the development of the face processing system. The developmental prosopagnosia case of YT (Bentin, Deouell & Soroker, 1999) provides data that suggest that the N170 can also be affected as the result of an abnormally developed system. YT is an individual with high IQ and ceiling performance on tests of visual perception such as the Benton Line Orientation test. However, his recognition of familiar faces is extremely impaired. Unfamiliar face recognition is also poor, as reflected by a low score on the Benton Facial recognition test (although it should still be noted that, unlike PHD, YT was in the normal range on this test albeit at the borderline level). Interestingly, YT's ERP waveform to faces was of normal

morphology, with normal amplitude of N170. However, like PHD, the N170 was not face sensitive. Unlike controls, there was no significant difference in N170 amplitude or latency to cars or furniture compared to faces. These results are limited due to the design of the testing procedure (e.g. the inversion effect was not tested) but at the very least they do indicate that the specificity of the N170 can be reduced in developmental disorders of face processing. For this reason, the specificity of N170 in Williams Syndrome will be investigated in the following chapters.

As already discussed in previous sections, structural encoding of faces undergoes a protracted course of development before the appearance of adult-like abilities. This is reflected in the developmental progression of the N170 component. Taylor and colleagues have published two papers documenting changes in the N170 from 4 to 15 years of age (Taylor, McCarthy, Saliba & Degiovanni, 1999; Taylor, Edmonds, McCarthy & Allison, 2001). The first study (Taylor et al., 1999) assessed the N170 at one temporal electrode over each hemisphere (T5 and T6) to faces, cars, scrambled faces, scrambled cars, and butterflies. These were the same stimuli as those used by Bentin (Bentin et al., 1996). The task was also the same and simply involved a button press to the butterfly targets. There were a number of important results:

- An N170 was evoked to faces at all ages, but often not to the other stimuli,
- Peak latency decreased linearly with age up to adulthood,
- Peak amplitude to faces but not other stimuli increased with age.

These data show that the development of face processing continues through adolescence and up to adulthood. There is no evidence of a qualitative shift in processing. However, the increase in amplitude with age was only significant for the RH, which could suggest that it is configural rather than featural processing that undergoes the most extensive development. The second published study by the same group attempted to tackle this issue in greater detail by presenting stimuli including upright and inverted faces to a similar cross-sectional group of children as in the

previous experiment. Unfortunately, it is unclear whether data were recorded from the same or anterior electrode sites. However, as would be predicted on the basis of behavioural and adult ERP results, the inverted stimuli N170 increased more in amplitude with age than did that to upright faces (although the inversion effect difference in latency was mature by 8 years of age). Also, as could be predicted, the N170 to both faces and inverted faces was larger on the left than the right in younger children but became more right lateralised at around 14-15 years. This study, then, supports at least two previous claims, first that face encoding changes over development, and second, that it is reflected in asymmetries in both left versus right hemisphere, and responses to upright versus inverted face stimuli. Importantly, it also illustrates the sensitivity of the electrophysiological technique over that of behavioural methods. ERPs can demonstrate that the development of face processing continues into late adolescence, some years after behavioural methods assume mature functioning.

It is essential to note that the N170 is just one component of the ERP waveform, though it is the most consistently face sensitive. It is often described in isolation but is in reality situated between two positive peaks, the P1 peaking at around 100-120 ms and P2 peaking around 200-220ms. The P1 peak preceding the N170 has also been documented as displaying some age-specific and stimulus effects. For example, in the Taylor et al. study just described, the P1 decreased in latency with age and showed bigger amplitude and shorter latencies for faces compared to other stimuli across all ages. These data support those using the MEG (Magnetoencephalography) technique in adults, in which the P1 has displayed a shorter latency to faces (Linkenkaer-Hansen, Palva, Sams, Hietanen, Aronen et al., 1998). This probably reflects an increase in attention to face compared to other stimuli. In non-face studies the latency and amplitude of the P1 has been demonstrated to be affected in both children and adults by, amongst other things, attention (Taylor & Khan, 2000). However, although the P1 may be modulated by attention in some circumstances, it clearly also reflects some of the most basic visual processes in visual areas such as

V2-V4. It was reported by Mangun to be the earliest ERP correlate of endogenous processing of visual stimuli (Mangun, 1995).

P2 effects have been infrequently documented. However, a recent paper posits a role for the component as the first stage in post-encoding face processing (Halit, de Haan & Johnson, 2000). Two studies are reported. In the first, ERPs are recorded in response to a single set of faces that differ in configuration across conditions by virtue of being 'stretched' to various degrees. Amplitude modulations were found for both the P1 and P2 components. The authors suggest that the P1 effects are probably attributable to differences in attention caused by systematic differences (due to stretching) in the attractiveness, or 'typicality' of the faces. This is supported by the second study which investigates responses to natural differences in typicality (stimuli which naturally differ in attractiveness and identity). In contrast, P2 modulations appear to be identity specific and not affected by changes in typicality. Interestingly, further support is given for the characterisation of the N170 as a pre-recognition encoder. Its amplitude was bigger for atypical faces for which configurational encoding would be more difficult, but completely unaffected by identity. In other words, the P2 appears to be the first ERP index of face identity recognition.

1.6 Chapter Summary

Face processing may be divided into at least two functions, structural encoding and recognition. Cognitive, neuropsychological, and brain imaging research support this distinction. Encoding of faces is different to the encoding of other stimuli, as it depends more on configural rather than featural information. Differences between the encoding of faces compared to other visual stimuli are already apparent at or near to birth in the typical case and become progressively more so over development at least until adulthood. Some researchers claim that 'face processing' is an innate module. This is not the case. Both encoding and recognition develop in interaction with experience. However, it is likely that face encoding *becomes* modularised in the sense that it is localised and domain-specific by adulthood.

The N170 ERP component is highly sensitive to face encoding, revealing an inversion effect to faces but not other stimuli. Its specificity is disrupted in prosopagnosia. In the typical case the N170 is now well characterised. It can reveal progressive cortico-electrical specialisation over developmental time. It is, therefore, an ideal component to investigate the structural encoding of faces in the case of atypical development.

Chapter Two

Williams

Syndrome

2 Williams Syndrome

2.1 Introduction

The investigation of face processing in Williams Syndrome is an unusual choice for research on atypical populations because it focuses on a domain of cognitive functioning that appears unimpaired at the behavioural level. Studies of atypical development usually focus on impairment e.g. the social, or 'theory of mind', deficit in autism. However, WS is interesting to the cognitive neuroscientist because there are purported dissociations between 'impaired' and 'intact' cognitive abilities. Most people with WS show relatively good performance on face processing tests, yet are very poor at visuospatial tasks e.g. (Bellugi, Sabo & Vaid, 1988). This dissociation at the behavioural level has been taken by some to reflect the difference in functioning between intact and impaired cognitive modules. As a consequence, WS has been used to support the claim that the brain has an innate modular structure . The deletion of individual or groups of genes is claimed to cause the impairment of individual cognitive modules (Pinker, 1994).

Hypotheses of innate modularity in WS can only be empirically falsified by investigating the supposed preserved module in the syndrome (Karmiloff-Smith, Grant, Berthoud, Davies, Howlin et al., 1997). In order to do this it should be shown that the cognitive and / or cortical processes mediating successful test behaviours are different to those of typically developing controls. Recent cognitive studies of face processing (discussed below) have attempted to show that this is the case. In short, they have found that people with WS systematically use different strategies compared to typically developing individuals, but still produce similar test accuracy scores. Yet if a module is 'intact,' then it should function in exactly the same way in WS as is does in typical development. These data suggest that face recognition performance in WS is not mediated by an intact module, and therefore cannot justifiably be used to support claims of innate modularity of the human brain.

Chapter One revealed that face processing in the typical case is not modular in the Fodorian sense, although in the typical adult it is supported by mechanisms that are likely to have become specialised for faces over development. The function that is most clearly face-specific is configural encoding. No work has yet been carried out to specifically investigate this early stage of face processing in Williams Syndrome. It is possible that good face recognition of individuals with WS is because of an 'intact' early mechanism, which is followed by a deficit in the retrieval of information from memory. It is equally possible that the encoding and perception of all visual stimuli, including faces, has developed atypically in WS.

In this section the characteristic features of Williams Syndrome are outlined, before detailed discussion of visuo-perceptual and face processing abilities. A number of hypotheses and research questions are then advanced. These will provide the focus for the following experimental chapters.

2.2 Physical Phenotype

Williams Syndrome is a rare disorder affecting approximately 1 in 20,000 live births (Martin, Snodgrass & Cohen, 1984; Arnold, Yule & Martin, 1985; Morris, Demsey, Leonard, Dilts & Blackburn, 1988). The most striking physical characteristic of WS is elfin facies (Joseph & Parrott, 1958). This is the typical facial dysmorphology of wide mouth, heavy orbital ridge, temporal dimples, retrousse nose with flat bridge and flared nostrils, stellate iris pattern, and irregular dentition. Mean birthweight is low, and there is typically serious delay in reaching motor milestones. Infants are often poor feeders who show a failure to thrive, along with gastrointestinal symptoms such as constipation and rectal prolapse (Morris et al., 1988). Although, initially thought to be diagnostic, hypercalcaemia affects only a small percentage of infants and can be treated by dietary intervention. Most people with WS (85-95% of individuals with the disorder) suffer from an abnormal hypersensitivity to sound, called hyperacusis (Marriage, 1994). Later in development, individuals with the syndrome are also likely to suffer from early puberty and premature aging (Cherniske, Sadler, Schwartz, Carpenter & Pober, 1999).

WS causes cardiac and vascular abnormalities in at least 75% of those afflicted (Donnai & Karmiloff-Smith, 2000). The most common problems are supravalvular aortic stenosis (SVAS), pulmonary artery stenosis, and high blood pressure. Less frequently (18%) the renal tract is also affected. Mild visual abnormalities are also common. Approximately 50% of people with WS have strabismus, which is usually corrected in early infancy. There has been found to be no relationship between early visual problems and visuospatial functioning in WS (Atkinson, Anker, Braddick, Nokes, Mason et al., 2001).

2.3 Personality

Data from questionnaire studies indicate that people with WS show higher rates of emotional and behavioural disturbance than people with other mental handicaps (Preus, 1984; Udwin, Yule & Martin, 1987). They tend to exhibit overactivity and poor concentration, excessive anxiety and poor relationships with peers. However, they are also reported to be overly friendly and socially disinhibited with other adults (Udwin et al., 1987; Einfeld, Tonge & Rees, 2001). Parents often report that children make much use of affective language, are very empathic, and are responsive to the emotional states of others (Bellugi, Adolphs, Cassady & Chiles, 1999). Experimental studies have suggested that socio-cognitive comprehension is poor, while socio-perceptual comprehension is relatively good (Tager-Flusberg, Boshart & Baron-Cohen, 1998).

2.4 Neuroanatomy

Magnetic Resonance Imaging (MRI) has been used to investigate neuroanatomy in WS. People with the syndrome are reported to have reduced overall brain, brain stem and cerebral volumes, with relatively normal cerebellar (especially neocerebellar) and superior temporal gyrus volumes (Galaburda & Bellugi, 2000; Reiss, Eliez, Schmitt, Straus, Lai et al., 2000). There is also a greater ratio of frontal to posterior (parietal and occipital) tissue compared to controls. Cerebral white

matter is disproportionately reduced in volume, as is grey matter in the right occipital lobe. In contrast, the grey matter of the parietal lobe is increased in volume.

Analysis has been carried out on autopsied brains of those with WS (Galaburda & Bellugi, 2000). Galaburda and Bellugi report a study that is consistent with the MRI results. Small brains (roughly the overall size of those with Down Syndrome) with parietal and occipital hypoplasia were noted. One of the most consistent findings across four subjects was a curtailment of the central sulcus. In a typical brain this sulcus proceeds dorsomedially to end beyond the interhemispheric fissure surface of the hemisphere. In WS the central sulcus ends abruptly before it reaches the midline. Architectonic observations, however, reveal that most gyral folding is relatively normal. All cortical regions sampled were architectonically normal, and Brodmanns areas identifiable. Histological analysis revealed no clear effects but much larger variability in cell packing densities in the WS group, particularly in layers 4 and 6. The authors claim this may reflect a disturbance in neuronal migration. There was a slight trend for cell packing density in controls to be greater than that of the WS group. The effects of any of these abnormalities on brain function and brain conductivity are as yet unknown.

2.5 Neurochemistry

Some attempt has been made to identify abnormalities of biochemistry in WS using the Magnetic Resonance Spectroscopy (MRS) technique (Rae, Karmiloff-Smith, Lee, Dixon, Grant et al., 1998). Increases in Cho/NA and Cre/NA but not Cho/Cre have been found, and are thought to be caused by a decrease in the neuronal marker N-acetylaspartate in WS compared to controls. The changes in resonance may be due to differences in neuronal density or mitochondrial synthesis of N-acetylaspartate, and may reflect decreased neurone viability and dysfunctional neuronal connections. The MRS measures support the view that neuronal orientation and packing are affected in WS. The effects of abnormalities of brain biochemistry are not fully known, but must be considered in the search for explanations of the WS cognitive phenotype.

2.6 Genetics

Williams Syndrome is diagnosed using a FISH test for microdeletion at the elastin locus on chromosome 7 (Ewart, Morris, Atkinson, Jin, Sternes et al., 1993). The deletion appears to be spontaneous, is not related to the age of the parents, and happens equally often on the maternally and paternally derived chromosomes (Donnai & Karmiloff-Smith, 2000). It is haploin-sufficiency of the elastin deletion that contributes to the cause of SVAS. The elasticity of the skin, lungs and blood vessels depend on the presence of elastic fibres. The ELN gene, which is expressed in the third trimester of pre-natal and first months of post-natal life, codes for a protein that makes up part of these fibres. However, the ELN deletion is not sufficient to cause all of the physical and cognitive characteristics of WS (Tassabehji, Metcalfe, Donnai, Hurst, Reardon et al., 1997). Repeats have been identified which contain other genes and pseudogenes, at either side of the deletion breakpoints (Robinson, Waslynka, Bernasconi, Wang, Clark et al., 1996).

LIM Kinase-1 (LIMK1), has been found to be deleted in the majority patients tested with WS (Frangiskakis et al., 1996; Tassabehji et al., 1996). This is a gene which encodes a protein involved in actin depolymerisation and recycling, which could be involved in axonal guidance during the development of the central nervous system in the retina, cortex, spinal cord, cranial nerves and dorsal root ganglia (Tassabehji, Metcalfe, Karmiloff-Smith, Carette, Grant et al., 1999). Initially Frangiskakis and colleagues (Frangiskakis et al., 1996) argued that the hemizygosity of LIMK1 caused the impaired visuspatial constructive cognition typical of WS. However, further studies from a different research group (Tassabehji et al., 1999) showed that LIMK1 deletion alone was not causal. They tested three individuals with SVAS who had the LIMK1 deletion and found no deficit in spatial cognition. This study makes it clear that there is probably a highly complex relationship between genotype and phenotype that does not just apply to the effects of LIMK1 deletion. The probability of discovering a direct link between any genes and cognition is extremely low, and possible effects are likely to be manifest only on low level cognitive processes that

have differing effects on different domains as development proceeds (Karmiloff-Smith, 1998; Johnson et al., In Press).

2.7 Cognitive Phenotype

As already discussed, Williams Syndrome is characterised by an uneven profile of cognitive abilities. General measures usually diagnose mild to moderate mental retardation, but with surprising islets of normal or near-normal ability in language and face processing. Disability is usually evident on tasks requiring number, motor, problem-solving, and planning, as well as visuospatial skills.

2.7.1 Language Ability

Language is one of the domains of ability that has often been claimed to be intact in WS. However, recent studies suggest that it is unlikely that any aspect, from syntax through to phonology, is truly unimpaired (Karmiloff-Smith et al., 1997). For example, Clahsen and Almazan (Clahsen & Almazan, 1998) claimed that grammar is spared in the syndrome, despite memory for vocabulary being impaired. In response, a different group (Thomas, Grant, Gsodl, Laing, Barham et al., 2000) conducted a much larger study (N=21 compared to N=4) which compared performance of the WS individuals to that of four different typical control groups at cross-sections over the trajectory of normal development. It was found that when the results were controlled for verbal mental age, the WS group showed no selective impairment or sparing of different aspects of language. In other words, no aspect of language behaviour was worse or better than would be expected given overall language development. It is not the case that some language modules are intact. In addition, other studies have shown that language behaviour is not only delayed, but the course of cognitive development is actually different to controls. For example, people with WS use pointing after they start naming things (Mervis, Morris, Bertrand & Robinson, 1999; Laing, Hulme, Grant & Karmiloff-Smith, 2001) whereas typically developing children do the opposite, and children with WS show an unusual sensitivity to the sound of language over meaning (Grant, Karmiloff-Smith, Gathercole, Paterson, Howlin et al., 1997). So, even when overt behaviour is

relatively good, the underlying cognitive systems appear to undergo abnormal trajectories of development. The hypothesis is that the brain pursues the same functional goal as in typical development (i.e. fluent language) by developing unusual neural mechanisms (following a different path). As will be discussed later, the same hypothesis applies to face processing.

ERPs have been used to ascertain whether language areas have developed differently in the brains of those with Williams Syndrome (Neville, Mills & Bellugi, 1994). The results confirm that at least some fundamental aspects are atypical. Over temporal areas, the early components that the authors label 'P50' and 'P200' were enlarged, and the N100 was decreased in size. This was true for all WS individuals compared to age-matched controls. For typical controls, open-classed words (mostly conveying meaning) elicit an N400 which is larger over the posterior right hemisphere. In contrast, closed class words (mostly conveying grammatical information) elicit an N400 which is more anterior, earlier in latency and lateralised to the left . People with WS showed no differences between these classes of words, and all N400 components were more lateralised to the left. These results suggest abnormal cortical organisation of these language functions in WS, despite the apparently 'normal' performance on behavioural tasks testing such abilities.

2.8 Visuospatial Cognition

The tasks that elicit poorest performance from people with WS are those testing visuospatial ability. People with WS have been found to be worse than chronological age (CA) and mental age (MA) matched controls on many standardised tests of visuospatial cognition: the block design subtest of the Weschler Intelligence Scale for Children-Revised (WISC-R), Differential Ability Scale (DAS), and British Ability Scales (BAS)(Bellugi, 1988; Crisco, Dobbs & Mulhern, 1988; Bellugi, Bihrle, Jernigan, Trauner & Doherty, 1990; Udwin & Yule, 1991b; Bellugi, Bihrle, Neville, Jernigan & Doherty, 1992; Bellugi, Wang & Jernigan, 1994; Karmiloff-Smith, 1998; Bellugi, Lichtenberger, Jones, Lai & St George, 2000); the visual recognition, discrimination, visual closure, and visual memory subtests of the

Illinois Test of Psycholingustic Abilities (Crisco et al., 1988); the Benton Line Orientation test (Bellugi et al., 1988; Wang, Doherty, Rourke & Bellugi, 1995; Karmiloff-Smith, 1997); the Developmental Test of Visuo-motor Integration (Bellugi et al., 1994); and the Delis Hierarchical Processing Test (Bihrle, Bellugi, Delis & Marks, 1989).

The dissociation in WS between relatively good language and very poor visuospatial behavioural performance is important. Neuropsychological studies of individuals with brain damage have demonstrated that the underlying cognitive and neural systems have a fairly high degree of independence, even to the extent that they are predominantly subserved by different cerebral hemispheres (Stiles & Nass, 1991). However, it is not clear whether the *development* of verbal and visuospatial systems is independent. For example, in WS it is possible that these systems are independent (e.g., as the expression of different sets of genes), that one system expands at the expense of the other, or that one system compensates for the anomalies of the other. Little is currently known as to how the development of different cognitive domains interact in typical children or in WS. It is clear now that language is not an 'intact' module in the disorder, but further research may be able to help answer more complex questions about brain development and plasticity.

Before embarking on a consideration of the 'dissociation' between visuospatial and other abilities, it is important to characterise precisely the WS impairment in this domain. There is significant controversy about which stages or components are actually affected (differently developed). Visuospatial ability is composed of a number of sub-components, which are more or less taxed depending on task. In the WS literature, however, the primary distinction is found between visuo-perception and visuo-spatial construction. Although this terminology is rarely (and inconsistently) defined, perception refers to the ability to see and encode a visual array. It is difficult to test behaviourally, but is most commonly indexed by matching or same / different tasks. In contrast, visuospatial construction is the ability to see an object or array and to construct a replica of it. This is easy to test, using tasks such as

the block design subtest which can be systematically manipulated for difficulty (see below). Clearly these skills are hierarchically related; it would be impossible to construct a pattern that was not perceived or encoded. However, some argue that it is visuospatial constructive cognition alone that is poor in WS (Mervis, Robinson & Pani, 1999), while others maintain that impairments exist at both levels (Bellugi et al., 2000). One goal of the present thesis is to determine whether the early perceptual stage is indeed intact. If encoding of visuo-spatial information is catastrophically disrupted then, contrary to previous claims, it is proposed that (using the WS literature terminology) it is 'perception' that is fundamentally impaired. If this is the case then it is impossible to assess the adult endstate for the effect a perceptual impairment has had on the development of visuo-construction skills.

There are limitations on the use of measures of behavioural performance on standardised tasks. Test scores are rarely informative about the nature of the cognitive mechanisms leading to such performance. In order to find out what is atypical about WS processing, a finer-grained analysis of the task requirements and the individual's processing style is required. Such analysis has shown that even within the domain of visuospatial ability there is a non-uniform pattern of performance. The most consistent abnormality noted is a difficulty with 'configural' processing. This was first documented by Bellugi and colleagues (Bellugi et al., 1988), in their analysis of block design performance.

The block design subtest of the WISC-R and WAIS-R, and pattern construction subtest of the BAS and DAS are very similar and have all been used with WS populations. In short, the participant is given a target design picture of a patterned square, which can be copied using the faces of coloured cubes. For example, in the WAIS-R, each cube has 2 red sides, 2 white sides, and 2 sides that are diagonally divided between red and white (the pattern construction subtest of the BAS and DAS begins at a slightly easier level using 2D blocks). The number of cubes required increases throughout the test. The edges of the cubes are not demarcated on the design that the participant is given. The participant must select the appropriate

surface of the blocks, and also arrange them in the correct configuration. Bellugi (Bellugi et al., 1994) found that people with WS had a particular difficulty in adhering to the global configuration of the pattern to be copied. Instead, the performance of people with WS showed a bias that favoured the details of the design. They used a '…fragmented piecemeal approach, never gaining the correct overall configuration, requiring multiple trials even on simple designs, including many counterproductive isolating movements…and trying to talk their way though the task', (Bellugi et al., 1994). Many studies since have attempted to investigate this hypothesis. Again, there is controversy about whether and where in the processing stream such bias exists. The evidence is discussed below.

2.8.1 Visuospatial Perception

The Benton Line Orientation task (Benton, Hamsher, Varney & Spreen, 1983a) is the most popular test of visuospatial perception. Participants are asked to match angular orientations of two simultaneously presented lines to those in a display of 11 lines oriented 18 degrees apart (to make a fan shape). Each target match can be identified by number or by pointing by the participant. People with WS are typically at floor on this test. For example, in results reported by Bellugi, (Bellugi et al., 1990), 80% of participants failed the preliminary practice items and the test itself was not even administered. However, the test is difficult and a comparison group of Down's syndrome participants, matched for CA and global IQ, were also at floor. Nonetheless it is worth noting that this task tests perception of configuration. Simply identifying a feature, (i.e. a line) is not sufficient for successful performance because all features are identical except for their relationship to the whole. An inability to encode configural information is, then, one explanation for the failure of people with WS on the task.

A featural processing style hypothesis is supported by results from a different kind of standardised task. The canonical/noncanonical views test requires identification from photos of real objects in common or in unusual orientations (Bellugi et al., 1988). Bellugi reports that people with WS perform significantly better than

people with Down's syndrome on the noncanonical (unusual) views. The test relies on featural identification. For example, for an upside down teapot photographed from above, identification is usually hindered by the appearance of the features in an unusual configuration. However, for individuals with WS, the identification of the spout of a teapot, despite its unusual context, was enough for a positive recognition response, suggesting little interference was caused by the unsual configuration. In addition, poor performance has been noted on tasks that require the opposite skill. Bellugi et al., (Bellugi et al., 1988) and Crisco et al., (Crisco et al., 1988) report that people with WS perform poorly on visual closure tests (of non-face stimuli). These tasks require participants to identify incomplete, familiar objects embedded in a distracting background, and to pay attention to the whole rather than only to the features.

Only two direct tests of local versus global perception have hirthto been published. (although in a book chapter, Bellugi and colleagues (Bihrle et al., 1989) refer briefly to an unpublished study, ' In perceptual matching tasks as well, Williams participants showed a local bias'. There is no further report of this experiment to date). In the first published study, Deruelle and her colleagues (Deruelle, Mancini, Livet, Casse-Perrot & de Schonen, 1999) used a match-to-sample task in which a simple pattern target stimulus or distractor differed at either the configural or the local level. Configural transformations were apriori defined as those involving the spatial relationships between the elements, and local transformations as those involving the shape of these elements. Two types of trial were used: an 'identity matching ' and a 'similarity matching to sample'. In the identity matching trials, the same pattern as the target was presented simultaneously with another pattern which differed either in configuration or local elements. In the similarity matching, neither of the choice stimuli were identical, but one differed from the target in configuration, and the other in local elements. A group of 12 individuals with WS (age range 7 to 23) were compared with both a control group matched on CA, and a group ('MA') matched on global IQ. The results showed that overall level of performance in WS was at the level of the MA controls, but within this equivalent

performance the WS group made more errors on configuration trials than either group. However, when the task involved detecting a local difference, the WS group performed as well as the CA and MA group. The CA and MA groups on both tasks detected more configural than local differences. This study confirms that perception of configuration in WS is indeed poor. It supports the hypothesis that people with WS are biased to process local over configural information.

The finding of deficit in the processing of configural information has recently been replicated in a series of experiments at the Neurocognitive Development Unit (Humphreys, 2000). Humphreys tested the same adults with Williams Syndrome that will be tested in the current thesis. In one of the experiments, participants were simultaneously presented with a target and two possible matches. One of the matches was identical and one differed either in configuration (increased distance between elements) or features (changed shape from squares to diamonds of same size). The results are displayed in Figure 2.1. There was a highly significant deficit in correctly identifying configural, but not featural (local), changes to the stimuli. Other experiments, investigating processing style preference and the effects of memory delay (no effect) supported these findings. Reaction time results mirrored those for accuracy.

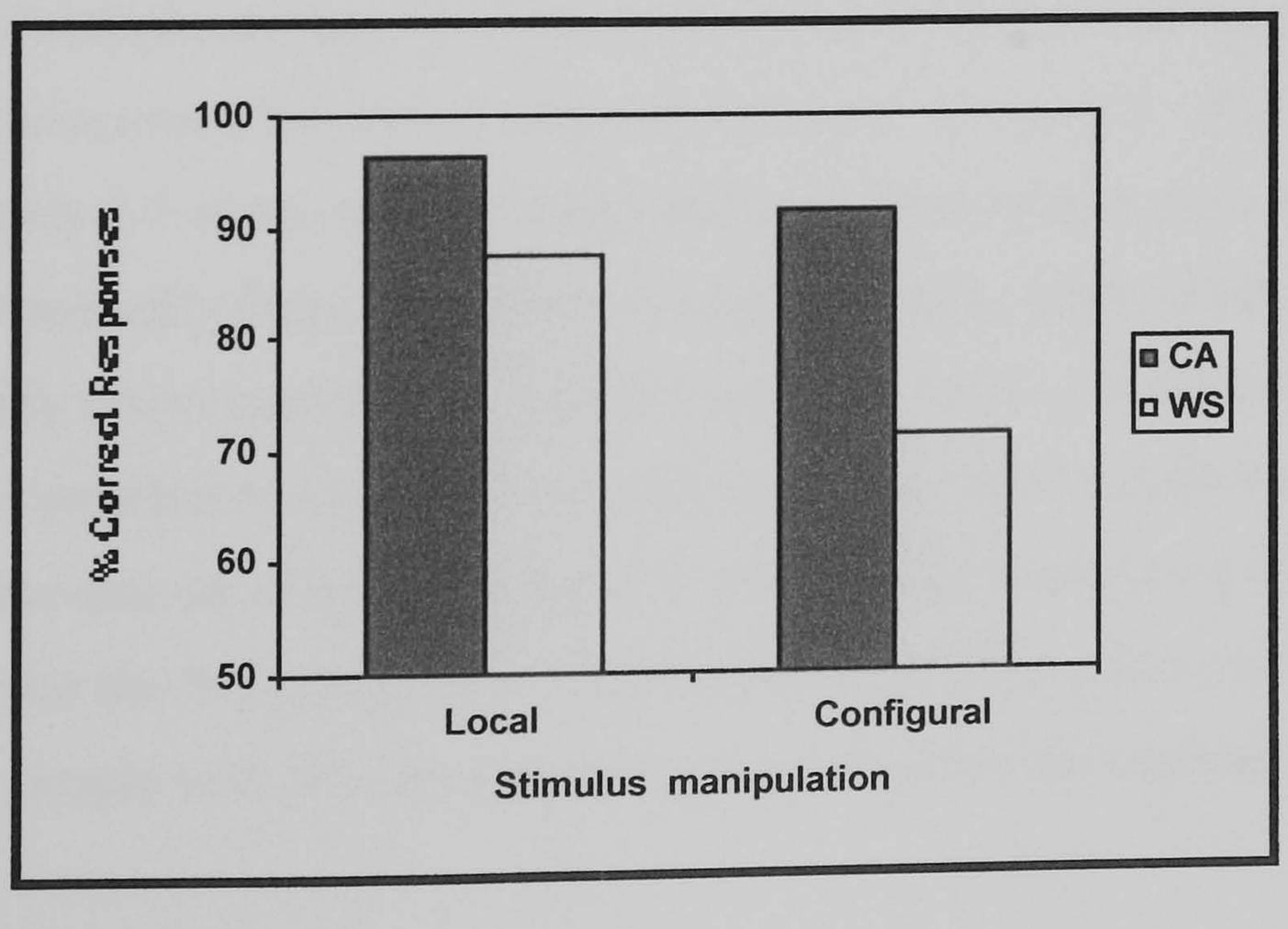


Figure 2.1 Accuracy on Behavioural Face Task (Humphreys, 2000)

The results of the Dereulle et al. (1999) and Humphreys (2000) experiments are in sharp contrast to those reported by Pani and colleagues (Pani, Mervis & Robinson, 1999). These authors used a visual search task to investigate whether spontaneous global perception of distractor stimuli would have a typical interference effect on the search for a target. Participants were asked to search for a letter amongst identical nonsense letter distractors that were similar in form to the target. The distractors were arranged so that they made up a 'whole' shape like an X or a triangle. The target was either 'hidden' within the resulting shape or isolated from it and located in another area of the screen. Studies with typical adults have shown that it takes longer to identify a target submerged as a component within a holistic figure than when it is isolated from it. This is presumed to be because of the primacy of global perception of the holistic figure, which either distracts the participant from the features contained within it, or automatically groups the distractor features so that the isolated target can be more quickly identified.

Pani et al. (1999) found that adults with WS were overall about twice as slow as a group of CA controls on their visual search task. In addition, the WS group did appear to be subject to the same global interference effect. The authors claim, however, that people with WS were not only affected by the gestalt of the figure, but they were abnormally unable to disengage from the global configuration when the task required local processing. This conclusion is based on the finding that although the RT patterns across trials were found to be the same as controls, the trials (comprising only 1/5 of the total) in which the target was submerged in a holistic figure took abnormally long. This is not an obvious finding when observing these data graphically (there appear to be no differences in pattern compared to controls), and involved complicated transformations of the data to reach significant results. However, these data are clear in that there is some gestalt interference effect on reaction time for the WS group. This is obviously an exciting finding because it suggests that people with WS can process a global figure at the expense of its parts.

The method used by Pani and colleagues (Pani et al., 1999) was subject to several limitations. For example, the size of the stimuli were tiny at only 1.5cm by 1cm each, with all of the stimuli very closely grouped into an array of only 5.5cm by 4cm. Size has been shown to have an important effect on grouping of stimuli in visual search tasks (Humphreys, Quinlan & Riddoch, 1989). Although the expected effects are observed for the control group, a better test for the WS group may have been to use larger stimuli. In addition, accuracy rate differences between trials are not reported (although mean accuracy levels compared to controls across all conditions are). It is possible that differences in RT may be confounded by different levels of accuracy between conditions. It is also possible that the group difference is due to an inadequate control group comparison. A group of MA-matched controls would be necessary to confirm that the apparent increase in interference when tasks demands are changed is due to a problem with switching perceptual style, and not just slower processing in general. It is unclear why the assumption should be made that RT increases linearly with decreasing IQ, and the effects of other factors like the changing task demands should remain constant in their effects.

The findings from the Pani et al. (1999) and Deruelle et al. (1999) tasks call into question the exact nature of the WS visuospatial problem. In the literature to date there has been no distinction made between the processing of configuration, as the specific spatial distances between parts, versus the processing of 'gestalt' or 'whole' information which could be defined as the overall arrangement of parts. The clearest example of this is the case of a face stimulus. It is possible that an individual may be able to perceive that the face is a face on the basis of the crude prototypical arrangement of parts (eyes above mouth above nose etc.), but not be able to encode the specific spatial distances between those parts that enable a typical individual to quickly differentiate one face from another. This may also be the case with other visual stimuli. For example, people with WS may be able to encode highly familiar shapes such as squares or crosses (such as were used on the Pani et al. task) but would not be able to differentiate between two such stimuli made up of the same parts but with different spatial distances between the parts.

In summary, most indirect and direct tests of perception in WS suggest that there is a specific deficit in processing the configural properties of stimuli. Further experiments using different kinds of tasks, and measuring both reaction time and accuracy, are required to elucidate further the exact nature and extent of this perceptual difference. In addition a refinement of terminology is critical. The Dereulle et al. (Deruelle et al., 1999) tasks, and the Benton Line orientation task require processing of configural properties of the array, that is the spatial arrangements of the elements. These tasks do not manipulate 'holistic' or 'gestalt' processing, in contrast to the Pani et al. (Pani et al., 1999) task. Several hypotheses remain to be tested. For example people with WS may percieve the gestalt but be unable to explicitly use this representation to guide motor action. Alternatively, they may be able to process highly familiar simple shapes (such as the global shapes used in the Pani et al. task) but not less familiar or abstract shapes, or may be affected by gestalt but not normally sensitive to the spatial arrangement of features within it.

2.9 Visuospatial Construction

As already described, the pattern construction / block design task is consistently found to be one of the areas of most difficulty for children, teenagers and adults with WS (Bellugi et al., 1988, 1990, 1994; Mervis, 1999; Udwin & Yule, 1991). For example, of 63 children and adults tested by Mervis and colleagues (Mervis, Morris et al., 1999) on the pattern construction subtest of the DAS, 85% of participants were in the first percentile.

The block design task has been investigated in typical development, and one modification that has been shown to make the task easier is to demarcate the block shapes in the pattern to be copied. This change to the task improves speed in typically developing adults and adolescents, and speed and accuracy of performance in adults and adolescents with mild mental retardation, as well as in typically developing young children (Royer, 1977; Shah & Frith, 1993). Mervis and colleagues (Mervis, Morris et al., 1999) hypothosised that if the poor performance of individuals with WS was due to a difficulty in dividing the global pattern into its

component parts, then the same form of modification should significantly improve performance. They found, as predicted, that accuracy improved, and RT decreased. They conclude that people with WS have difficulty with segmenting the whole into its component parts. This is, of course, surprising given the results on perceptual tasks which suggest quite the opposite problem. In addition, Mervis et al. do not compare the results to those of a control group. However, a recent study of the same manipulation to the block design task (Farran et al., 2000) did compare a WS group to a MA matched control group. These authors also made the task slightly easier by providing the outline of a square which the participants could use to guide the arrangement of the blocks (ensuring that the global outline of the design was correct and the blocks were not, for example, placed in a single line). The results of this study indicate that the individuals with WS were no more aided by the segmentation of the blocks than were the control group, and still performed at a significantly lower level. This suggests that the deficit is not an inability to segment the whole, or indeed an inability to arrange blocks into the correct global shape, but an inability to percieve or use configural information (that is the information about the spatial relations between the parts). In other words, the specific difficulty is in orienting a block in the correct spatial location compared to the other blocks. This would support the research on direct tests of perception. It suggests that it is the perceptual ability, rather than the confounding constructive ability, that most affects block design performance in WS.

An alternative method to test visuoconstructive ability is to use tasks in which participants are asked to reproduce particular patterns by drawing. Bellugi et al. (1990) noted that when asked to draw a simple everyday object such as a bicycle, people with WS produced drawings that were unidentifiable and failed to integrate the parts into a whole. They also perform poorly on standardised tasks such as the Delis Hierarchical Processing Test (Delis, Kiefner, & Fridlund, 1988). In this task each pattern to be copied is composed of local elements which, when taken together, constitute a recognisable global form, e.g., small circles arranged in the shape of a large triangle. Birhle et al. (1989) found that in general people with WS tended to

correctly draw only the local elements of the stimulus, but did not arrange them into the correct overall configuration. This was in contrast to a group of people with DS who displayed the opposite profile of producing the overall form but not the local elements. More recently, Bertrand and colleagues (Bertrand, Mervis & Eisenberg, 2001) compared the drawing abilities of a young group of WS participants to both a group of MA and CA controls. They showed that compared to either group, the children with WS failed to integrate components into the appropriate overall configuration. However, they claim that this is because people with WS are delayed in drawing development, and in fact follow the same developmental trends as typically developing children. The study was longitudinal and showed improvements in the drawings of the WS group that broadly mirrored those of much younger CA and MA typically developing controls. These results may again suggest that the visuoperception in WS is differently developed to that of controls whereas visuo-construction follows a more typical developmental path.

In summary, visuospatial construction, like perception, is poor in WS due to difficulty in processing configural information. However, there does appear to be some improvement in aspects of construction, such as drawing, over time. It is currently unclear whether an abnormality in the perception / encoding of configural information can entirely account for visuo-construction problems or whether additional abnormalities in the other domains (such as visuo-motor co-ordination), or general developmental delay, affect construction.

2.10 Face Processing

People with WS typically enjoy looking at faces, and WS infants spend abnormally long periods of time gazing at faces (Bellugi et al., 2000). This is often reported by parents and clinicians. The tendency to fixate on the experimenter's face is a sometimes unnerving feature of testing children and adults with the disorder. Despite, or perhaps because of, this attention to faces, people with Williams Syndrome are usually good at face recognition. Indeed, many have claimed that face processing is 'selectively preserved' or 'spared' in Williams Syndrome (Bellugi et

al., 1988; Udwin & Yule, 1991a; Bellugi et al., 1994; Wang et al., 1995). This modular account of WS brain functioning is based on the normal or near-normal behavioural performance of WS individuals on standardised face recognition tests. An example of one such test is the Benton Test of Facial Recognition (Benton, Hamsher, Varney & Spreen, 1983b). Participants are asked to match a target face to either one or three of six faces in an array displayed below the target face. The faces are greyscale photographs of unfamiliar faces across viewed from different angles and across different lighting conditions. People with WS typically score significantly higher than would be expected from their overall MA, or performance in other domains of visuospatial functioning, and often fall within the normal range (Bellugi et al., 1988; Bellugi et al., 1992; Bellugi et al., 1994; Wang et al., 1995; Karmiloff-Smith, 1997; Jones, Hickok & Lai, 1998; Pezzini, Vicari, Volterra, Milani & Ossella, 1999). This high level of performance is also reflected in other neuropsychological face processing assessment measures such as The Rivermead Behavioural Memory Test (Udwin & Yule, 1991a).

The assertion of 'intact' modularity of face processing in WS is surprising given what is now known of typical brain development (see Preamble and Chapter One). Good face processing is not unexpected according to a modular account of brain development, because modules are thought to be innately specified and neurally distinct from the processing of other stimuli. However, according to the neuroconstructivist view it is unexpected because of the nature of the visuospatial difficulties in WS. As discussed in the previous sections, it is the encoding of configural rather than featural information that appears to be particularly impaired in WS visual processing. Yet face processing in the typical case depends much more than object processing on the successful encoding of configural information. The perplexing nature of the WS profile could be explained in a multitude of ways. For example, some of the possibilities are a) that face processing is an independent, genetically specified module which remains intact regardless of the state of other modules; or b) that face processing is far from independent, and develops configural encoding at the expense of the visuospatial system or; c) that the face processing

system may also have developed differently, like the visuospatial system, but has become expert at processing faces using this alternative processing system or; d) that face processing mechanism has not developed and the WS brain becomes highly experienced with using a featural object processing system to process faces.

If the face encoding 'module' is intact in WS, then it should function in the same way as that of a typically developing individual. One of the hallmarks of a typically developed face encoding system is that it is significantly affected by the inversion of a face stimulus (see Chapter One). This is thought to be because of the reliance on configural information. However, people with WS have been shown to have a specific deficit in encoding configural information for non-face visual patterns. If the face 'module' develops independently from the object processing system, then it may be able to engage in the normal encoding of configural information. Alternatively, if it is the object system (or a module developed from the object system) that is used to process faces, then there should be a specific deficit in the configural encoding of faces as well as non-faces.

At present the behavioural evidence on the inversion effect in Williams Syndrome is mixed. An early study strongly suggested that there was no inversion effect for faces in WS (Rossen, Jones, Wang & klima, 1995). This was supported by a thorough investigation by Deruelle et al., (Deruelle et al., 1999). The second experiment in a series by these authors compared the inversion effect for faces compared to houses, with the prediction that an inversion effect should occur with faces but not houses for the MA and CA control groups. For the WS group the prediction was that they would adopt a local mode of processing and therefore neither faces nor houses would be subject to an inversion effect. The task required a same/different response via a keyboard press from the participant, and both stimuli to be assessed were presented on a computer screen simultaneously. Overall, the WS group performed at the level of the MA matches. However, as predicted, and unlike the MA match or CA groups, they were not subject to an inversion effect in the face condition. Also as predicted, there was no inversion effect for any of the groups on the house stimuli.

These data support the hypothesis that people with WS rely less on configural information for face encoding than do typical controls.

The results of Deruelle at al. are in contrast to those of Jones and colleagues (Jones et al., 1998). These authors presented participants with upright face stimuli and then required them to search an array of inverted faces for a match. The results showed a surprising increase in the inversion effect for WS children compared to typical CA controls. However, the task was a difficult one that required not only search skills but memory and mental rotation ability. These factors probably explain the difference between the two findings. This was not the case with an experiment carried out by Mills and colleagues (Mills, Alvarez, St George, Appelbaum, Bellugi et al., 2000). These authors found an inversion effect in WS adults similar to that of typical adults, but the design of the experiment was compromised by the requirement to measure both ERP and behavioural data concurrently. In their task the participant was presented with one face for 1.5 seconds, followed by the presentation of a same or different face in the same orientation after an interval of 1 second. This delay was necessary in order to record late ERP effects, but introduces a confounding memory component to the task. It is possible that people with WS are equally good at differentiating between two upright or inverted face exemplars but are worse at remembering inverted faces. Perhaps the inverted face is less interesting to the WS individual than the upright face, and consequently is less well attended and memorised. Alternatively the differences between the results of Deruelle et al. and Mills et al. may reflect the difference in performance of a group which contained children compared to one comprised solely of adults. In other words, it may be that the inversion effect just develops slowly in WS children and develops to an atypical degree in WS adults. Longitudinal studies, or those that sample cross-sectionally across development are necessary to answer this debate decisively.

The configural deficit for faces has been investigated using experiments other than those manipulating orientation of the stimulus. Karmiloff-Smith (Karmiloff-Smith,

1997) used a range of face matching tasks with a WS group compared to MA matched controls. These tasks required participants to match faces on the basis of identity, emotional expression, gaze direction, or lip reading. Performance varied across these trials, and the author suggests that those trials on which the WS group performed best were those on which a featural or componential mode of analysis was optimal (e.g. lip-reading). Conversely, those trials on which the performance of the WS group was poorest were those which required configural processing (e.g. identity matching faces in different orientations). However, (as the author recognised) the analysis was post-hoc, because the experiment did not directly manipulate configural or featural information. It was, however, subsequently supported by the results of Deruelle et al. (1999) using similar stimuli. In addition, these authors note that WS face processing, unlike that of typical controls, does not improve with age. There was no correlation in the WS group (7 to 23 years of age) between age and accuracy. This is highly unusual compared to typical development, and rules out a simple 'delay' explanation of the configural processing impairment. Delay suggests the progression of ability but with a time-lag between the WS group and the typically developing comparison group. In contrast, these data indicate that by the age of 7 years the WS system may have reached in atypical ceiling on face processing development.

Electrophysiology of Face Processing

The behavioural evidence described above has already suggested that face processing in WS is far from being a 'spared' module. This conclusion is supported by the results of an ERP study attempting to examine the functional organisation of brain systems linked to face recognition (Mills et al., 2000). In this study, ERPs were recorded from 14 sites modified from the standard 10/20 system, and referenced to linked mastoids. Participants were required to watch pairs of upright or inverted faces that were presented sequentially (1000ms ISI) on a computer screen. They were then asked to indicate by button press whether the second presented face was the same or different from the first.

The results of this study are difficult to interpret, not least because there were no explicit predictions for the ERPs of the WS group. The authors conducted an average of 16 analyses (ANOVAs on latency and amplitude) for each of 4 components, separately for the first and second face presentation, in 2 different scalp areas. These investigated group, hemisphere, orientation, and electrode site interactions. The authors then report correlations between behavioural data (experimental and Benton Test of Face Recognition) and the various ERP components. This large number of analyses highlights one of the problems of ERP research. Without explicit hypotheses there are potentially thousands of possible effects to investigate and report, despite the likelihood of one effect in twenty (assuming an alpha of .05) resulting from chance.

The Mills et al., (2000) study was designed to investigate the recognition of faces. However, the most 'strikingly different' waveform characteristics compared to controls occurred within the first 200ms after stimulus onset (N100 and N200), and thus are more likely to reflect encoding or perceptual processing than recognition. EEG was not recorded from sites (e.g. Temporal areas such as T5 and T6) likely to detect the N170 face-sensitive component. Nonetheless, overall the N100 was abnormally small and the N200 abnormally large. The N100 also tended (albeit non-significantly) peak later for the WS group. Both components did show an effect of inversion, the N200 being larger and the N100 being smaller and earlier in both groups for upright compared to inverted faces. The N200 was both larger and 12ms later for the WS group. Over all components there was non-significantly less RH activation, and more LH activation for the WS group compared to controls.

Previous results for typical adults on match/mismatch face recognition tasks had shown differences in waveforms for upright versus inverted face recognition. Upright faces when mismatched gave rise to a negativity over the RH anterior electrode at 320ms. In contrast, inverted faces when mismatched gave rise to a bilateral posterior positivity at 500ms. The same task used with typically developing children (9 to 16 years of age) elicited no waveform differences for mismatched

faces nor hemispheric lateralisation. In the Mills et al. (2000) study, the match / mismatch effect at 320ms was also significant in both WS and typical groups. The effect was, however, larger for participants with WS. The authors claim that the results taken as a whole show that the brain systems that mediate perception in WS are highly abnormal, and those that mediate face recognition are organised normally but developmentally delayed. This is because the N320 match / mismatch effect is mostly similar over all electrodes for the WS compared to the typically developing adult control group, and ERPs at a latency of 320ms are likely to reflect recognition rather than encoding processes.

In contrast to later effects, the early ERPs thought to index perception, the N100 and N200, are abnormal in latency and amplitude in WS. In addition a larger N200 was elicited for those participants who scored higher on the Benton test of Facial recognition (Benton et al., 1983b). Mills et al. claim that the abnormal size of these components may be 'markers' for WS. For the purposes of this thesis, it is the early components that are of greatest interest. These data would support those from behavioural studies, in suggesting that even at the very earliest stages of visual processing there are differences between people with WS and typical controls. They suggest that further ERP studies should concentrate specifically on early perceptual processes, to elucidate exactly what functional differences may be implicated. Unfortunately it is not possible to relate the results of the Mills et al. experiment to most other studies of face perception, particularly those investigating the N170 face-sensitive component because, as already pointed out, the standard temporal recording sites were not used. The authors do, however, state that further work should be carried out to investigate the N170 component in Williams Syndrome. In addition further work should be carried out, first to compare ERPs to faces to those elicited by other visual stimuli, and second to compare ERPs of WS adults to those of WS children.

Summary of Face Processing in WS

Behavioural and electrophysiological studies suggest that face processing is not 'intact' in WS, but that it develops differently compared to controls. Although face matching ability is higher overall than would be expected from visuospatial ability, the processing style is abnormal. This appears to be because people with WS engage in less configural encoding than typical controls. The hypothesis is that Williams Syndrome impairs the ability to encode the spatial relationships between facial features.

2.11 Hypotheses

What is hirtherto known about visuospatial and face processing in Williams Syndrome has been fully described. However, the number of attempts in the literature to *explain* the WS profile have been severely limited. In this section, a number of hypotheses (of non-orthogonal and potentially interacting abnormalities) are considered, before the research questions to be pursued in the current thesis are outlined.

2.11.1 Vision

The most simple explanation is that early visual deficits such as strabismus, visual acuity loss, amblyopia, or reduced stereopsis, cause the visuospatial problems in WS. This hypothesis has been considered in detail by Atkinson and colleagues (Atkinson et al., 2001). These authors have tested a large number of children with WS on both sensory visual tasks and visuo-cognitive tasks. They document an increase in the incidence of sensory-visual problems in the WS population compared to typically developing individuals but find no relationship between the two sensory and visuo-cognitive measures. Indeed, Atkinson (Atkinson, 2000) states that at the individual level, her research group have found children without any visual deficits who show severe visuospatial impairment, and children with marked visual impairment who show much milder visuospatial difficulties. In addition, it would be hard to argue that visuo-sensory impairments could cause face processing to become a domain of successful functioning. If poor visual acuity, for example, were at fault,

then the prediction should be of a configural advantage, because this is the information contained in the low spatial frequencies.

2.11.2 Right Hemisphere

The domain of most successful functioning in WS is probably language, and the least successful is the visuospatial domain. In typical development, these functions have been shown to be largely supported by opposite hemispheres, with right hemisphere (RH) damage having most effect on visuospatial processing (Stiles & Thal, 1993). Right hemisphere damage can be seen at its most extreme in the case of adults who suffer brain insult such as stroke (particularly to parietal lobe). This sometimes gives rise to contra-lateral 'neglect' in which the left-side of space ceases to 'exist' for the individual. There is no current evidence to support a 'neglect' hypothesis in WS (Wang et al., 1995). However, another feature of such lesions is the tendency towards part-based processing. For example, on tests such as the Delis Hierarchical Processing test, children and adults with RH lesions tend to copy the details without arranging them into the correct configuration (Delis, Kiefner & Fridlund, 1988). As mentioned earlier, this behaviour has been documented in WS on the same task. However, caution should be exercised in making such a comparison, as a lack of integration in drawing is also documented in very young typically developing children. Longitudinal analysis suggestes that integration in drawing improves with age in WS, and follows a similar path, albeit with massive delay, to that of typical children (Bertrand et al., 2001).

A right hemisphere lesion hypothesis is simple, but there is no evidence of such a lesion from imaging or autopsy of WS brains (Galaburda & Bellugi, 2000). Also, the 'knocking out' of specific functions is unlikely to be found, given what is now known about brain development and the nature of developmental disorders (see Preamble). Nonetheless, this does not mean that a RH hypothesis should be completely discarded. It is possible that the neural networks of the WS brain are for some reason 'biased' toward left hemisphere functions. To date, all functional imaging studies of visuospatial and language processing in WS have documented

some abnormality of lateralisation to the LH, despite a lack of structural abnormality of the RH (Neville et al., 1994; Mills et al., 2000). It is also interesting to note that throughout typical development, face encoding is usually more right than left lateralised. For this reason, abnormal lateralisation should be further considered in the current thesis studies of WS brain function.

2.11.3 Dorsal Stream

A different possible candidate abnormality is of the dorsal stream in WS. In the typical development literature, two visual 'streams' or pathways progressing from the primary visual cortex have been proposed (Mishkin, Ungerleider & Macko, 1983; Milner & Goodale, 1995). These are claimed to encode different types of information. The developmentally later dorsal stream carries information about spatial relationships ('where'). In contrast the ventral stream ('what' and 'how'), emerging earlier in development, encodes information about action and motion (although the functional distinctions may be overly crude, they are widely used). A classic function attributed to the ventral stream, which runs to the temporal lobe, is face recognition.

There is some evidence in WS for a selective deficit in functions thought to reflect the dorsal stream. For example, Atkinson's research group (Atkinson, King, Braddick, Nokes, Anker et al., 1997) has investigated the detection of coherent global motion when presented in the midst of random noise. An important part of the dorsal (and not ventral) stream is visual area V5 (MT). The neurons in this area are highly sensitive to motion coherence. Thresholds were tested in WS individuals. The findings were compared to results of a ventral stream task in which the processing of static form (concentric patterns of vertical line segments in random noise) designed to stimulate ventral area V4 were used. The authors claim that the motion coherence thresholds were abnormally high for WS children, and were like much younger (around 4 years of age) controls. In contrast, many results for the ventral task were within the normal range for chronological age. The authors also investigated the performance of children with WS on a 'postbox' task (Milner & Goodale, 1995)

designed to test the visual guidance of action (dorsal stream). Here, too, evidence was found to support a dorsal stream disadvantage. However, all tasks displayed a very large degree of variation within the WS group as although many individuals performed poorly, a substantial portion of individuals scored within the normal range. For this reason, as the authors concede, these data should be interpreted with caution.

Despite the WS relative success on the 'ventral stream' tasks designed by the Atkinson group, there are reasons to suggest that the ventral stream is far from intact. Face processing is a classic ventral stream function, and the behavioural success on face tasks has been assumed to reflect intact functioning. As has already been discussed at length, this is not the case. However, the electrophysiological characteristics of WS temporal lobe processing have not been investigated. The studies in the current thesis will investigate the time differences in ventral-stream-type functioning for WS compared to typical individuals on a millisecond by millisecond basis. This method can highlight the point in time at which WS processing begins to vary.

2.11.4 Atypical Modularisation

Chapter One discussed the development of face encoding from infancy to adult. The developmental picture portrayed here is one where a subcortical detector system ensures high face input to an unspecified cortical visual encoding network. The network eventually specialises in the RH to form a face encoding 'module' which detects faces on the basis of configuration. The processing of such a 'structural encoder' is reflected in the N170 ERP component. The hallmark of this developed system is a significant inversion effect in amplitude and latency to faces, but not other objects. The core goal of the current thesis is to investigate the possible modularisation of function in WS, using the N170 and associated early ERP components.

As mentioned earlier, there are a huge number of possible differences between the WS and typical systems, and in discussing potential abnormalities it is impossible to be entirely comprehensive. However, the current brain imaging data is inadequate to refute the claim that face encoding in WS is an independent, genetically specified module which remains intact regardless of the state of other modules. If this is the case, then the N170 should be normal in morphology and topography to faces but possibly not objects, and its processing should be typically affected by inversion. In addition, the N170 should be specialised in being much larger for faces compared to other visual stimuli. It should also follow a developmental trajectory that is similar to that of typical controls.

An alternative view is that face processing in WS is not an independent module and develops at the expense of the visuospatial system. The result of this kind of development is difficult to predict. There may be ERP evidence for an organised response to faces, from a large area of cortex, which to other stimuli is disorganised or more topographically marginalised. The prediction may also be that as development progresses the more organised the response to faces, the more disordered the response to other stimuli will be. In contrast, it may be that all visual processing in WS is underdeveloped, and that the face processing mechanism has not modularised. Relatively good face recognition behaviour may be achieved because of the high input of faces to the system, due to the interest in faces shown by people with WS. Another prediction is that the whole visual encoding system in WS has undergone an atypical developmental trajectory, resulting in idiosyncratic effects that are unique to the syndrome. In this case, investigation of the N170 across WS development, and across syndromes, should highlight these differences.

2.11.5 Research Questions

The goal of this thesis is to explore the encoding of faces in Williams Syndrome, in order to investigate the specialisation (and 'modularisation') of brain function in the disorder. To this end, there were a number of initial research questions that the following experiments attempt to address:

- Are the electrophysiological correlates of early (before 200ms) face processing 'spared' in WS? This question is investigated by comparing the WS adult end-state to that of typical adult controls. The prediction is that the P1-N170-P2 complex and gamma-band bursting will both show differences in morphology compared to controls.
- Does face processing follow an abnormal trajectory? The adult waveform components are compared to those of younger WS participants and their controls. The prediction is that the N170 will not look ' developmentally delayed', but will show evidence of developing differently compared to typically developing controls.
- Are the differences specific to WS? The adult waveforms are compared to those of an autistic group. The prediction is that atypicalities of the N170 and gamma band bursting will be syndrome-specific.
- Are they specific to face processing? Waveforms across the WS trajectory, and their controls, are compared to those obtained from non-human-face visual stimuli. The prediction is that the N170 will be less specialised (stimulus specific) than the highly specialised N170 of typically developing controls.
- Finally, how do electrophysiological differences relate to what is known of visual processing differences in WS? Processing demands are manipulated within each experiment in order to assess the contributing effects of stimulus parts versus configuration. The prediction is that the N170 and gamma-band bursting of the WS group will fail to show the human-face inversion effect. In addition the WS group N170 will be unlike that of typically developing controls and fail to show differences between stimuli composed of the same parts in different configurations.

Chapter Three

Methods

3 Methods

3.1 Introduction to ERP Method

The theoretical approach and research questions already outlined require the use of a technique that satisfies several criteria. It must: (i) focus on temporal dynamics, (ii) be suitable for use with participants of all IQ and age ranges, (iii) be non-invasive, (iv) give information about very early processing, and (v) be already used in a literature on typical development in which this research could be situated. ERPs (Event-Related Potentials) are the only brain imaging method that satisfy all of these requirements. This section outlines what ERPs are, and how to obtain, analyse and interpret them.

The electroencephalogram (EEG) is the amplified recording, over time, of voltage differences between 'active' and 'reference' electrodes. Electrodes are attached to the scalp, with the reference in a site 'neutral' to those of interest to the particular focus of the research. The waveforms are composed of a number of different sine waves within identifiable frequency bands (alpha, beta, delta, theta, gamma). The event-related potential (ERP) comprises all frequencies represented as a single band, and is obtained from an epoch of EEG which is time-locked to an event, such as the onset or offset of a stimulus, or a button press. The epoch is usually defined with a baseline period (e.g. –200ms to 0ms), an event onset (0ms), and a response period (e.g.0-900ms). The ERP consists of the voltage changes that are thought to be specifically related to the brain's response to the specific stimulus.

3.1.1 The Signal

The relationship between the brain and scalp electrical activity remains opaque. However, it is thought that the EEG primarily reflects dendritic potentials (i.e., post-synaptic rather than axonal action potentials (Allison, Wood & McCarthy, 1996)) and it is known that some conditions must be satisfied in order that these potentials be measured at the scalp. These requirements refer to the necessary size,

synchronicity and configuration of the neuronal assemblies generating the electrical field. In other words, the neuronal populations must be large, synchronously active, and configured to produce a dipolar field. This means that individual neurons must be oriented in parallel with positive and negative charges aligned (the dipolar field), like tiny batteries, to allow current to flow. Fortunately, the cortex is mostly arranged into the necessary 'open fields' (while most 'lower' brain structures are not).

3.1.2 Obtaining the Signal

The EEG recording consists of relative, not absolute values. Voltage change at an experimental electrode is only valid at a particular time point if the voltage at the reference electrode remains constant. It is clear, then, that the choice of reference is vital to the interpretation of the resulting waveform. Popular recording practice is to employ a single 'common' reference electrode, or linked pair of electrodes, in an area uninfluenced by the electrical activity of interest, e.g., on the mastoid bone behind the ear. Some researchers then take a further step and re-calculate values off-line in relation to the 'average reference' consisting of the mean value of all electrodes at each time point (see 'extracting the signal' below).

Standard locations exist for electrode placement. Traditionally the 10-20 system (Jasper, 1958) is used. In this system, electrode sites are described with a letter corresponding to the proximity to particular areas of the brain, together with a number which is odd for left, even for right, and the subscript z for midline. For example, Fz refers to frontal midline and T5 refers to a left posterior temporal area. The 10-20 terminology is still current, although recently a new standard '10-10' international system has been accepted (Chatrian, Lettich & Nelson, 1985) which has a larger number (74) of electrode sites. This may soon be surpassed by a 10-5 system that labels as many as 345 electrode locations (Oostenveld & Praamstra, 2001). One reason that a new labelling system is required is because of the use of high-density electrode recording systems such as the 'geodesic net' (Tucker, 1993)

which can have up to 256 electrodes. When publishing high density ERP (HD-ERP) results, it is usual to present waveforms from sites on the 10-20 system, or to describe locations with reference to these standard sites (Picton, Bentin, Berg, Donchin, Hillyard et al., 2000).

Geodesic sensor nets have a number of advantages (many of which are shared with other high-density systems), apart from the obvious improvement in spatial resolution. On a practical level, all electrodes are regularly spaced, being connected together by thin plastic cords. A few key measurements are taken to determine the central point of the participant's head. The net can be applied, with the electrodes in the correct sites, in less than five minutes. In contrast to previous methods, no fixing glue is required, so the whole procedure is far quicker for the experimenter and more comfortable for the participant. For the safety of the participant, all sensor nets are completely isolated from the mains supply and the mains supply ground. The input amplifiers are connected to an 'isolated common' or ground electrode fitted on the net.

Before recording, the experimenter must stipulate the gain and sampling rate, and adjust the set-up for optimal recording. The broad gain determines the conversion of the analog signal to amplified digital values. It is usually set to around an amplification of 10,000 for each 1μv. The sampling rate is the number of these values recorded per second. Sampling rates should be high enough to capture without distortion the activity in the highest frequency band of interest. The higher the frequency band the higher should be the sampling rate (the sampling rate must be more than twice the rate of the highest frequency). One of the drawbacks of the higher rates is that they result in larger files that take up significant disc space. Also before every recording the amplifier should be calibrated. This is achieved by sending sine waves of a known amplitude to the amplifier to measure 'gains', and also measuring the 'zero' which is how much the zero weight of the amplifier deviates from its previous weight. The 'impedance', which is the resistance to

electrical current existing at the scalp, can then be measured and, if necessary, the sensor net adjusted to increase contact and decrease resistance.

3.1.3 Extracting the Signal

The event-related temporal segments of EEG must be processed in order to extract the signal from noise. The first step in noise reduction is to reject artefactual activity resulting from unwanted eye or muscle movement (e.g. tongue or scalp). It is important to note in this respect that the eyeball itself functions like an electrical dipole (Rugg & Coles, 1995). The positive and negative charges at either side produce contaminating electrical fields, which propagate back across the head when the eyes are moved. In order to reduce these artefacts, participants are instructed to attend to a fixation point during ERP recording. In some studies participants are further instructed to blink only between stimulus presentations. However, this imposes an extra task upon the participant which may have amplifying or distorting effects on some components (Ochoa & Polich, 2000). It is also impractical for some very young or clinical groups who may lack the ocular control and/or understanding to comply with such instruction. In any case, all recordings should also be investigated off-line for potential contamination.

Off-line artefact removal can be achieved in one of three ways. Artefacts can be discarded by visual inspection, trial by trial, or by an automated procedure which removes trials in which activity surpasses cut-off amplitudes. Alternatively, algorithms can be applied which adjust the data to remove the contaminating effects. The latter has the advantage that most eye-blink trials can be retained. However, there is some controversy about its use (Barrett, 2000). Automatic rejection by 'cut-off' criteria has the potential disadvantage of participant loss due to insufficient artefact- free trials, but the advantage of including only 'pure' trials. Rejection by eye (the method used for the data presented in this thesis) has the additional advantage that the experimenter receives a 'feel' for the representative quality of the final waveform when signal extraction is complete. It is a technique that is frequently used with young and clinical groups and is often complimented with

videotape recordings of the participant's behaviour during testing. Videos are analysed off-line to ensure that the participant was actually attending to each trial. Rejection is then carried out for those trials where the participant was not complying, but which may not be represented by movement artefacts (e.g. several trials spent looking at the floor and not at the computer monitor).

Filtering is the second step that may be used to attenuate artefactual activity. The EEG often contains frequencies that are outside those of interest to the experimenter or generated by sources other than the brain (e.g. mains frequency at 50-60Hz). For this reason, activity above (and below) certain frequencies is removed. Filtering has the effect of 'smoothing' the original waveform. This, by nature, distorts the waveform but the extent of distortion may become unacceptable if the filter is set to remove very low frequencies (Hillyard & Picton, 1987). Following de Haan and colleagues, (de Haan et al., 1998) the ERP data (except for gamma analysis, Chapter Seven) presented in this thesis were digitally filtered at 30Hz using an elliptical filter to limit artefactual spiking.

Segmented ERP data will contain some drift such that on different trials, the post-stimulus waveform starts from a different value. For this reason, a segment of baseline period, (activity prior to stimulus onset) is selected to adjust the amplitude of the following waveform. All waveforms in this thesis were tied to a baseline period 100ms prior to stimulus onset. This was achieved by subtracting the average baseline value from each individual time point of each electrode for each trial. The data for each electrode and trial were then averaged. Averaging is the most common method of signal extraction for ERPs. The EEG waveform changes are large, and they obscure the tiny (microvolt) changes that are related specifically to the experimental event. For this reason, all trials that correspond to the same experimental condition are averaged together, so that the resulting waveforms represent the mean activity for each electrode at each time point. The assumption behind this technique is that the 'background' activity unrelated to the event will

vary randomly across trials and average near to zero. Therefore, the higher the number of trials, the higher the signal to noise ratio.

The final averaged waveform should represent only activity that is temporally related to the stimulus in a consistent fashion. It is clear, however, that the averaged waveform could represent the individual trial data inaccurately. One potential hazard is 'latency jitter'. This means that the event-related activity begins or peaks at different latencies (times) over successive trials. The consequence is that the averaged waveform becomes distorted in shape and the amplitude is reduced in relation to the individual waveforms from which it is derived. Because of this, and other potential hazards (like bimodal distribution), different signal detection techniques have been explored. As yet, they are infrequently used except in analysis of induced high frequency responses (see Chapter Seven).

In most studies, at least one electrode will be rejected due to poor contact with the scalp or technical problems with the electrode. If more than 5-10% of electrodes lack an acceptable signal then the recording should be discarded. If it is to be retained, then the missing waveforms must be interpolated (Picton et al., 2000). This can be achieved employing either a linear algorithm which uses only the adjacent electrodes to approximate the data, or a spherical spline algorithm that uses all electrodes. The former has the limitation that distortions can occur if data from more than one electrode in a scalp area have been removed. For the current thesis, the interpolation of missing data was carried out using spherical spline interpolation.

In the current thesis, the final step used to prepare the ERP for analysis was re-referencing. As already described, the neutrality of the reference measure is essential to obtaining a representative waveform. The most appropriate measure will vary for each experiment but it is generally accepted that the average activity of all waveforms at each time point - the 'common average' (Picton et al., 2000)- is satisfactory for most studies (Dien, 1998). The result is that the original reference electrode (often Cz) is re-constructed (to represent the average scalp activity), and

used as reference for all other electrodes. This is the procedure used for the data presented here.

3.1.4 Describing the Signal

The ERP waveform is usually described in terms of the 'components' it contains. In most waveforms there will be a number of classical components that can be identified (e.g. the N170, see Chapter One). The simplest definition of a component is a clear peak or trough in the waveform. A label is given, together with a letter, P (positive) or N (negative), and a number corresponding either to the latency (post-stimulus onset) or to position in relation to other peaks of the same polarity (e.g. P1, N1, P2). The component can then be compared between conditions or groups in terms of its exact latency (ms) and amplitude (μv). Amplitude is measured either in relation to baseline or to another component of the waveform ('peak-to-peak').

The simple definition of the component described above has been rejected by some (Rugg & Coles, 1995) as merely the description of a 'deflection'. It is true that those conducting ERP research are rarely interested in the waveform deflections per se, but rather in what they may represent in terms of cognitive processing or physiological activity. This has lead to at least two other possible definitions of the component (for discussion of these issues and different approaches to definition see Rugg et al., 1995, pp 8-11). The physiological approach claims that the defining characteristic of a component should be its source in the brain. This position theoretically overcomes the problem of 'component overlap'. Due to the volume conduction properties of the brain, an ERP peak over one scalp area may actually be the summation of two or more fields from dipoles in different brain regions, which maximally peak before and after the observed peak. So the single deflection observed could be the result of spatially diffuse neural generators. As a result, the physiological position stipulates that likely sources should be identified before a component is characterised. However, while theoretically justifiable, this approach is difficult to implement in practice. Source localisation from ERPs is difficult and,

although techniques such as Brain Electrical Source Analysis (BESA) are improving, they are most useful when possible anatomical solutions are constrained by information from other functional imaging techniques and animal modeling. Such evidence, when available, is always indirect and consequently necessitates inferences that could result in misleading component identification.

The most extreme alternative is to take a 'psychological' approach to component identification (Rugg & Coles, 1995). From this perspective, it is the cognitive process involved that should define the component. However, given that many psychological functions are likely to occur in parallel, this is also a difficult approach to implement in practice. The feature of the waveform to distinguish is problematic because the obvious peaks or troughs may be the reflection of several different cognitive processes. The way to overcome this and objectively identify components has been subject to much research. For example, the idea of exploiting patterns of co-variation amongst the data using Principal Components Analysis (PCA) initially seemed like a good one. However, when applied to ERP, PCA tends to misallocate variance (Wood & McCarthy, 1984) and has some problems accepting latency differences between conditions. For this reason it has in the main been rejected, while research on different techniques continues.

One alternative solution to component identification is to use the subtraction method. This is an approach common to many neuroimaging techniques. It is based on the assumption that two experimental conditions can be designed to vary only by the cognitive process of interest. So, the subtraction of one brain measure from the other can be used to identify the activity attributable to that cognitive process alone. However, the legitimacy of this assumption has been questioned (Rugg & Coles, 1995). It is possible that when task conditions change, then activity associated with the 'supporting' operations may not be stable as presumed but also modified. As a consequence, a component should be described in terms of the psychological manipulation(s) that affect it, but not in terms of reflecting neural generators solely responsible for the hypothesised cognitive process evoked.

3.1.5 Analysing the Signal

Once the component of interest has been identified, it must be analysed to test whether apparent and/or predicted differences are statistically significant. The most common approach is to instruct specialist software to identify the amplitude and latency of the most negative or positive deflection within a specified time window. This is computed in batches, for each individual's average waveform at each electrode of interest. A time window is obtained by measuring the latency of the component in the grand average waveform and the waveforms of the most extreme participants for each condition (shortest and longest latencies). The window given is from extreme to extreme, in order to capture the component for each electrode and participant. This is a method that is sufficient for most components, except when some unusual conditions are present (as in the data presented in this thesis, see thesis methods section). In this instance each waveform must be investigated and component values noted by hand.

All analyses of differences in ERP data should be hypothesis driven. In the case of high-density sensor nets, the number of waveforms per subject means that some apparently significant differences could otherwise be identified by chance. To minimise the likelihood of such Type I error (or the possible Type II error as a result of Bonferroni correction to the alpha due to multiple comparisons), sensors are usually combined and component values averaged. Electrodes are grouped by spatial proximity in the scalp areas of interest. In the studies presented here, focus for statistical analysis was placed on occipito-temporal areas on the basis of previous studies. Electrodes were divided over these scalp sites into left and right hemispheres. Other topographical differences were noted on the basis of scalp voltage map comparisons.

Statistical issues plague the analysis of ERP data. The typical experiment aims to detect amplitude differences in the order of a few microvolts, and latency in the order of a few milliseconds. Groups, especially clinical groups, are often very small and variance, even amongst typically developing groups, is often high. These factors

mean that reliable differences are hard to find. Many studies use repeated measures ANOVA, which is fairly robust to violations of some assumptions, e.g., normal distribution (Howell, 1992). However, appropriate care is not always taken to ensure homogeneity of variance and equal cell numbers. Ideally, power analyses (to identify the number of participants necessary in order to attribute significance to the predicted difference) should also be carried out to determine the viability of the study based on available resources.

One statistical issue, raised by McCarthy and Wood (McCarthy & Wood, 1985), is important to the analysis of topographical changes. Consider two components from two experimental conditions / groups. The question is whether the components have the same or statistically different scalp distributions (and by implication, neural sources). The simplest solution is to enter location and condition into the same ANOVA. However, ANOVA is based on an additive model that is incompatible with the multiplicative effects of changes in source strength on ERP voltages. This means that a change in strength of the signal may be assumed to be a change in neural generators. As a consequence, data for condition x topographical analysis should be scaled (using the McCarthy *et al.* formula) to remove any differences in amplitude.

3.1.6 Displaying the Data

Analysis of the ERP component is essential but must be accompanied by some graphical representation of what was measured. ERPs can be displayed as voltage change over either time or space. Standard procedure is to present topographic maps at particular latencies, in addition to grand average waveforms, i.e., the average of all subjects' average waveforms. In this thesis waveforms are used to illustrate the morphology of the component for each group, and topographic amplitude maps are used to display relative amplitude over the head for particular components at particular time points. There is no current convention for representing polarity (although traditionally negative deflections are plotted upwards). However, for the data presented here, positive potentials are always plotted as upward deflections.

3.1.7 Assumptions

Once the waveform has been obtained, extracted, analysed and displayed, it must be interpreted. The interpretation of the waveform, and the acceptance of ERP as a method, depends on a number of assumptions (Rugg & Coles, 1995). The first is the assumption that can be termed 'physiological causation', that is, that cognitive operations are produced exclusively by neural processes. The logical extension of this position is that only one functional state can be associated with one physical state. In relation to ERPs, physiological causation can be interpreted as follows: the exact neural process causing ERP waveform A, at site A, can only be associated with cognitive process A, and not cognitive process B or C. This is correct in theory. However, in practice this could lead to error. It is possible that more than one combination of different neural generators, the action of which are only detected remotely as a conglomerate measure at the scalp, could produce visually homogenous waveforms as a result of different cognitive processes.

The practical problems of assuming physical causation severely constrain interpretation of null effects. If there are no differences between waveforms in two experimental conditions, it is not always permissible to conclude that the underlying brain activity was the same. Differences could remain undetected due to the configuration of tissue, or due to low amplitude or subcortical responses. Rugg *et al.*, (Rugg & Coles, 1995) prescribe power analyses for experiments predicting these null effects. Power analysis enables the researcher to plan an experiment of sufficient numbers to detect any meaningful difference should it exist (though this presumes that the size of 'meaningful' difference can be assessed prior to running the experiment). The reduction of Type 1 error risk is one advantage of high-density electrode nets and high sampling rates; the more measures taken, the higher the likelihood of detecting difference. Again, the importance of predictive hypotheses cannot be overstressed since HD-ERPS, in offering more sites for potential difference, do increase the converse possibility of committing a Type II error.

The second assumption can be termed the 'criterion' assumption, i.e., that some criteria must be assumed to decide when ERPs reflect qualitatively rather than quantitatively different processes (Rugg & Coles, 1995). Criteria can be decided on the basis of amplitude, latency, and topography. Take the hypothetical component A, measured in conditions (or at times) 1 and 2. The decision is whether the difference in component A^2 is caused by the same neural (and therefore functional) systems causing A^1, or whether a different system is responsible. It is generally assumed that if the difference is in amplitude alone then the same neural system working at different activation levels is responsible (Rugg & Coles, 1995). Amplitude along with topographical differences could be the result of the same system being active to different degrees or different systems being active (so data must be analysed after scaling, see Analysing the Signal above). Alternatively, the same system is thought to be involved if topography remains constant and latency alone is changed (providing all earlier components are equivalent in latency). The inference here is that the system for some reason was delayed in activation because of an increase in difficulty, for example. On the other hand, different systems are assumed if topography differs and latency remains constant, or if all factors differ. However, these criteria are general only, and are usually implicit in the literature. In reality results must be individually considered in the light of information regarding neural sources, obtained using complimentary techniques.

One of the problems inherent in the criterion assumption is that of significant difference, either between subject groups or neural sources. At what point can latency, amplitude or topography be considered to be different between conditions? Most assume that any significant difference is adequate regardless of the size (Rugg & Coles, 1995). When sampling from a large number of electrodes, the difference between conditions must be consistent across both electrodes and participants in order to be statistically significant. However, the inference may differ depending on the size of effect. For example, if the difference between A^1 and A^2 is 4ms, then all prior latencies being equal, a legitimate conclusion could be that the same functional mechanisms are involved in both cases. However, if this statistic was larger at 24ms

then it could be legitimate to infer different systems, especially if later components were clearly different in any way. These are issues that must be addressed in interpreting any ERP study, and again underline the importance of conducting hypothesis-driven research, which is (where possible) well grounded in the literature utilising alternative techniques.

The third assumption can be termed 'functional'. That is, that there is an assumed functional relationship between the neural activity reflected in an ERP component and the part played by that activity in relation to a specific cognitive process. This is highly dependent on the view of information processing taken by the researcher. It is simple to see how 'stage' models of information processing can be used, e.g., Bruce and Young's model of face recognition (Bruce, 1988). Each component is attributed to the workings of each consecutive stage, and experiments conducted to confirm or refute. This provides clear hypotheses for study. However, more recent models of information processing such as neural networks, which stress the importance of parallel processing, make such a relationship less clear. This is an issue which has received very little attention in the ERP literature. Its omission is in part due to the fourth assumption: that of 'correlation as causation'.

One of the most important methodological problems of ERPs is that there can only ever be an indirect *correlation* between components and cognition. The implicit assumption in the literature is that neural activity underlying the ERP waveform is the cause rather than the consequence of changes in cognitive activity. But it is also possible that changes in the waveform result from different processes that are affected by the one being manipulated. For example, changing the structural properties of a face stimulus can affect both amplitude and the latency of the N170 component (Eimer, 2000). However, it is possible in principle that the N170 may not directly reflect the activity of the system coding for the structural properties of faces but may reflect the neural activity of a mechanism affected by this processor. Changes in the stimulus can only ever be correlated with changes in the scalp activity and the participants' behaviour. This is of higher importance for some

studies than others. If the goal of the experiment is to find out what structural properties are discriminated, then it may be of less importance than if the goal is to discover the neural basis of the 'structural' processor. This problem is discussed by Rugg et al.. (Rugg & Coles, 1995). They point out that the same limitation is not only present in ERP research, but in all imaging studies. Only direct manipulation of neural systems can resolve these issues.

3.1.8 Interpretation

The assumptions underlying the ERP method have been discussed, but there are also specific inferences from waveform to cognition that merit attention. These are detailed in (Rugg & Coles, 1995). 'Interpretation' for most ERP studies involves deciding when differences in the waveform can be said to be the result of a change in neural sources. It also means deciding what functional factor causes any waveform difference (whether the neural source changes or is amplified and / or delayed). Here the inferential steps are made explicit using the N170 component as an example. The N170 is the component that will be the focus of the experimental chapters of the current thesis. It is essential that each logical stage is clear in the literature on typical development, because further inferences are to be made about the atypical case. Figure 3.1 is an example of an average occipito-temporal waveform from an experiment in which adults passively viewed human faces. The red line indicates the response to upright faces, and the blue line the response to inverted faces. The N170 component is indicated by the arrow.

1 The most limited conclusion to be made from Fig. 3.1 is that the upright and inverted stimuli have different effects on the amplitude and latency of the N170. This has been confirmed many times with statistical analysis (such as that to be presented in Chapter Four). The assumption is that the N170 represents neural activity related to processing of the stimulus. Since the waveforms differ, it can been inferred that processing is different or delayed for the inverted face.

2 The waveforms for the two conditions begin to differ sometime after the P1. The inference can then be made that at least by the point that the waveforms

separate, the neural processing in the two conditions is different or delayed in the inverted face condition. The latency at which the waveforms begin to separate is the upper limit. In other words, the processing of upright compared to inverted faces could begin to differ sometime earlier, but this fails to be reflected in the ERP. The latency difference provides constraints on the time-course of processing.

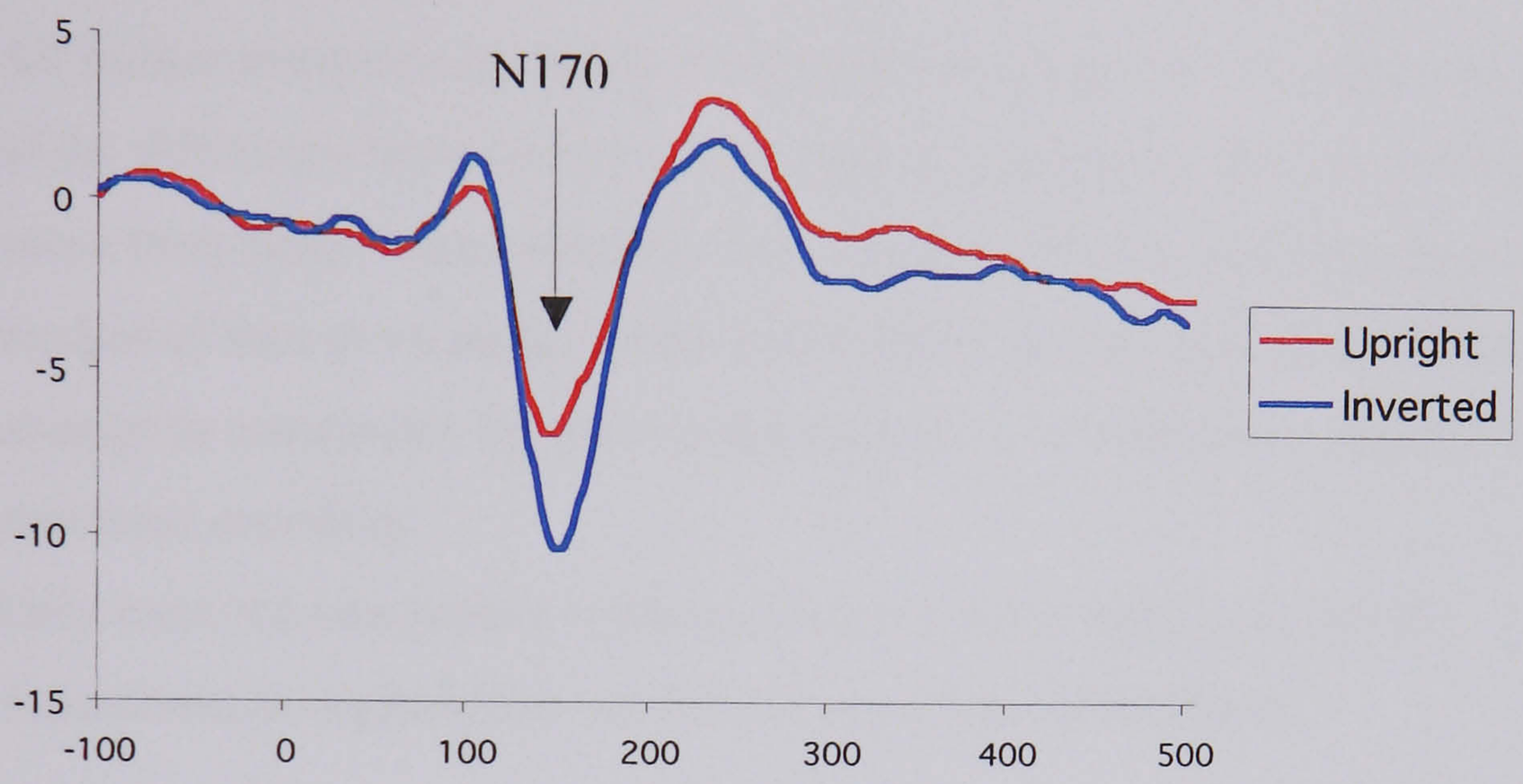


Figure 3.1 Example of N170 Waveform to Human Face Stimulus

3 The waveforms illustrated are those typical at and around electrodes T5 and T6. However, the entire scalp is sampled using the HD-ERP technique. It is possible that the waveforms in other areas are differentially activated in the same time course. For example, the waveform at electrode Cz could have a Vertex Positive Potential (VPP) component to the inverted face only. This parallel activation would give strong evidence that the inverted stimulus engaged neurally different (rather than delayed) processes, compared to the upright stimulus. This is not the case in practice. The VPP is present to both orientations and may reflect the inverse di-pole of the N170 (see Chapter One).

4 The scalp distribution of the component of interest is also important. The N170 is often larger over the RH than the LH. In addition, the difference between the upright compared to inverted face is commonly larger on the RH (although still

often significant on the LH). This may relate to the functional interpretation, for example it is the RH that is often implicated in configural processing in behavioural studies and other neuroimaging paradigms. Topography, in terms of focal area of activation, is typically very similar for each condition despite the increased amplitude to the inverted face. This suggests that similar neural generators are involved but to different extents. Dissimilar spatial topography, if present, could constitute evidence of different neural (and therefore functional) processes.

5 All further interpretation of the N170 difference depends on conceptual analysis of the difference between the upright and inverted face. This information can come from behavioural and other brain imaging studies, and from theoretical models of face processing. Other ERP studies are also important. These should attempt to manipulate the processing deemed to be reflected by the N170, e.g., structural encoding.

6 Only once the component is characterised in the normal case, can the experiment be legitimately conducted on atypical populations.

3.2 Thesis Methods

3.2.1 Study Design and Limitations

The testing of atypical populations offers a challenge to any study design. But the use of brain imaging equipment requiring a large number of trials and low percentage of movement artefacts makes the task even more difficult. The studies presented here were primarily limited by the low numbers of participants available, and the time restrictions inherent in testing them. Williams Syndrome is a rare disorder and the number of participants in each group in each study is very low. ERP experiments typically depend on around ten to twelve participants. The limited numbers here necessarily limit the conclusions that can be drawn.

One of the most enduring and difficult problems in research on developmental disorders is how to chose comparison or control groups. This also affected the

current studies because the neuroanatomy of the WS participants was known to be different from any other possible control. The solution chosen was to conduct only hypothesis-driven studies that focus as much on between condition (within group) comparisons as between group differences. This is well suited to the ERP technique. However, comparison groups were necessary, as normative data for cohorts of typically developing individuals were unavailable. The result was that several different groups were chosen. Initial testing on the Benton Face Recognition task confirmed previous research in finding that most of the WS individuals performed at a level typical of their chronological age (i.e., in the normal range). For this reason, typical controls were chosen who were individually matched on chronological age and sex to the WS group.

It is common in studies of developmental disorders to compare the experimental group to Mental Age (MA) matched controls. The rationale is that it is then possible to ascertain which behaviours of the experimental group are due to general delay as opposed to specific disorder of the behaviour in question. This is based on the assumption that some developmental disorders, or domains of ability in such disorders, may not be 'differently developed' but merely static at a stage of development which typical children pass through at a certain chronological age. The Interactive Specialisation Approach (Johnson, 2000), as outlined in the Introduction of the current thesis, fundamentally challenges this assumption. For general discussion about the use of MA comparisons, both of groups composed of younger CA children and of other supposedly 'purely delayed' rather than 'different' developmental disorders please see Burack, Hoddapp and Zigler (1998).

Mental age comparison groups were not used in the experiments presented in the current thesis for a number of reasons. First, as already mentioned, the WS group performed in the normal range on a standard face processing task despite their low MA on other neuropsychological measures. This made the choice of an MA comparison group difficult because if typically developing individuals were chosen matched on visuospatial or global measures then performance of face-processing

tasks such as the Benton would be far lower than for the WS group. It was possible that controls could have been found to match for verbal MA (which is always higher in the WS group than visuospatial or global MA) and Benton Face Recognition scores but the theoretical reason for chosing such controls would have been unclear. There is no literature to suggest that verbal MA is related to face processing. It is more likely that typically developing verbal MA matches would possess equivalent face processing skills because a) they would be much older than visuospatial controls, and face processing is known to improve dramatically with age, and b) verbal matches would have much higher visuospatial ability than the WS individuals (i.e. in line with their verbal MA). Because of all of these concerns, the role of MA was investigated without MA controls by the use of correlations between MA and ERP measures in the WS group.

The comparison of the adult WS group to typical adult controls was important but also of interest was the trajectory of development. The N170 normally undergoes a protracted course of change up to at least 18 years of age. For this reason, we chose an adolescent WS group with matched typical controls under the age of 18. Unfortunately a younger, or infant, WS group of sufficient size was beyond the scope of the project.

Adults with autism were chosen as an additional comparison group to the WS adults for the first study. This was in order to test the extent to which effects were syndrome specific. Autism is a disorder in which face processing is usually very poor, unlike that of WS which is usually relatively good. People with autism, like those with WS, have been found to show a reduced or absent face inversion effect and to be impaired on tasks requiring configural processing (Langdell, 1978; Hobson, Ouston & Lee, 1988; Tantam, Monaghan, Nicholson & Stirling, 1989; Volkmar, Sparrow, Rende & Cohen, 1989; Boucher & Lewis, 1992; Davies, Bishop, Manstead & Tantam, 1994; Teunisse & De Gelder, 1994; Boucher, Lewis & Collis, 1998; Klin, Sparrow, de Bildt, Cicchetti, Cohen et al., 1999; Schultz, Gauthier, Klin, Fulbright, Anderson et al., 2000). A featural processing style, or weak 'central

coherence', has been to used explain this poor performance (Frith, 1989). However, the same hypothesis has been used to explain the *good* behavioural performance of people with WS on face recognition tasks. Clearly both accounts cannot be correct in their current form. A broadly defined deficit in configural processing cannot be used to explain both successful and unsuccessful behavioural performances. It was hoped that the use electrophysiological measures would enable the processing style of WS and autism groups to be differentiated. High functioning individuals were chosen for this study because they were more likely to be amenable to testing than lower functioning. Such people generally have greater control over motor movements and are less likely to engage in repetitive motor stereotypies.

People with WS typically have mild to moderately low IQ and attention-span. We therefore used very simple passive-viewing or button-press studies that were within the capabilities of even the lowest IQ participant. Stimulus presentation (except for Kanizsa experiment, see Chapter Seven) was experimenter controlled in order to limit the number of lost trials due to inattention. Sessions were videotaped in order that attention could be monitored off-line. The number of conditions in each experiment was minimised, and the number of trials kept to around 100 per condition. This is the same number of trials successfully used with typically developing infants and adults in previous studies using the same paradigm (de Haan et al., 1998). Participants were monitored for anxiety or fatigue on-line throughout the sessions, and given breaks when necessary. People with WS can become acutely anxious, particularly in new situations (Udwin & Yule, 1991a). For this reason all participants were given a thorough explanation of the procedure and allowed to 'play' with the equipment (e.g. netting the experimenter or a parent and pretending to conduct the experiment) before the session took place. In addition, an experimenter or carer sat with the participant in the sound booth throughout the recording in order to offer re-assurance.

A potential hazard when recording EEG is the production of movement artefacts. High artefact levels often result in the loss of the participants' data, so this had to be

stringently monitored in the present studies where WS participants were particularly precious. All participants were instructed to 'try and keep as still as you can so that you can concentrate on the screen'. If the individual did begin to move or blink repeatedly, they were presented with visual distracters (moving coloured patterns on the screen) or given a break until they had settled again. These precautions lead to a very low participant loss rate. All procedures were conducted in exactly the same manner for all participants, regardless of diagnosis.

3.2.2 General Procedural Information

Some aspects of procedure and analysis varied between experiments, and these are reported in the individual study chapters. However, the majority of the procedure and analysis was common to all studies and is presented here, in order to avoid repetition.

Participants all gave informed written consent. This was in the presence of a carer for all those who did not travel to the session independently. The parent / carers consent was also required for all participants under 18 years of age. All participants were tested individually in a dimly lit, acoustically and electrically shielded sound booth. For the younger participants, and older participants who requested it, an experimenter or carer sat beside them throughout the testing session. The session was monitored and recorded by an experimenter external to the booth, via a video camera. If the participant showed any signs of anxiety or fatigue, the experiment was paused and the individual given a short break before recommencing.

EEG was recorded using a Geodesic Sensor Net of 128 silver-silver chloride electrodes, against a vertex reference, amplified with a broad gain of 10,000 and 0.1 to 100-Hz bandpass filtering. Electrical impedance at each electrode was kept below 50kΩ (Tucker, 1993). A ground electrode was positioned on the forehead, and electro-oculogram was recorded from an electrode placed above, below, and to the side of each eye. The recording was digitized at a 250-Hz sampling rate, stored on a

computer disk and segmented offline into epochs from 200-ms pre-stimulus to 900-ms post-stimulus onset.

3.2.3 General Data Analysis

Movement and electrical artefacts were identified and rejected by trial-by-trial inspection of the recorded EEG. Videotape recordings were also used for artefact rejection for those individuals (the youngest group of WS and controls only) who had been noted on-line to have difficulty attending to the task. Editing criteria were as follows: data from a sensor were excluded if i) they went off-scale; ii) the sensor was not making good contact with the scalp; iii) there was any activity clearly unrelated to brain activity (e.g. large amplitude, sharp deflections of 150μv or above). Data from a whole trial were excluded if: i) more than 12 sensors were excluded; ii) there was any eye-blink; or iii) there was any other eye or head / body movement. The remaining data were then filtered using a 30Hz digital elliptical filter before being baseline corrected (average voltage for 100ms pre-stimulus onset subtracted from the post-stimulus time-points). For each participant a separate average was created across the trials within each of the conditions. Finally, the data were interpolated using a spherical spline interpolation for any missing / inadeqate-trial sensors, before re-referencing to the average reference. Individuals with less than 24 valid artefact-free trials per condition were excluded from the study.

Statistical data for the waveform components of interest were calculated from the individual subject averages using the EGI Transave program. Time windows were the same for all groups and experiments. The window was chosen by measuring individual peaks for the same 3 individual electrodes (T5, T6 and O2) for each participant for each component for the human face experiment (the same procedure of checking the time window was adopted for all other experiments and was judged to be inclusive of all necessary peaks for all experiments). The extremes of these values were then used (minus 4ms from the lowest value and plus 4ms from the highest value in order to give a window to include all peaks). They were: P1, 60-160ms; N170, 108-228ms; P2, 188-284ms. These data were manually checked for

accuracy, by comparing the actual component amplitude and latency (for each electrode of each participant) to those identified by Transave. Accuracy checking was carried out because the latency to peak was very variable over all participants and the time window was very wide as a result. The Transave program identifies the most extreme value (of specified polarity) within the given window. If this time band is wide or if a negative component is positive in value then it may pick up a different peak to the one desired for some waveforms. For example, if the 'N170' is a very small deflection which is positive in value (as was the case for the adolescent group of WS participants), and the window is wide, then Transave may pick up the most negative value on the up-sweep of the P1 or the down-sweep of the P2 instead. This happens because although the N170 is clearly visible, it is not the most negative value within the time window. The number of corrections was stable across experiments with approximately 6% of values requiring hand adjustment.

Before analysis, data from selected individual electrodes were grouped according to hemisphere. They were then averaged to give a single data point for each hemisphere and participant. Electrodes were the same as those used in previous studies using the same stimuli (de Haan, Pascalis & Johnson, In press) and are illustrated in Figure 3.2. These electrode sites were in the region in which the N170 was maximal, and were also used in order have results directly comparable to previous studies of typical groups, using the same stimuli.

3.2.4 Statistical Analysis

Any data set can be analysed in a multitude of ways, depending on what is required of the analysis. Previous ERP experiments on which the present experiments are based consisted of one typically developing group who were tested on two conditions (de Haan et al., In press). Data from the relevant ERP component was then analysed separately for amplitude and latency. For each of these measures, a large repeated measures Analysis of Variance was carried out, with condition, hemisphere, electrode group etc. as within participant factors. The output contained every possible main effect and interaction, and all significant results were discussed

and interpreted, where necessary, with further post-hoc tests. This kind of analysis is suitable for datasets from large groups, with a limited number of factors to analyse. It was not suitable for the data presented in this thesis for a number of reasons:

- The number of participant groups (up to five)
- Unequal N between adolescent and adult groups
- Unequal variance between adolescent and adult groups
- Very small N in each group (low degrees of freedom)
- Potential for multiple comparisons meaning high chance of Type I (un-adjusted alpha) or Type II (family-wise alpha adjusted to take account of number of comparisons) error.

If data for all groups were included in the group factor of a large ANOVA then the resulting effects and interactions could be extremely difficult to interpret, and may require multiple post-hoc tests (such as t-tests). Multiple comparisons greatly increase the chance of making a Type I error (rejecting the null hypothesis when it is actually true), unless they are set-up apriori as predicted contrasts (Howell, 1992).

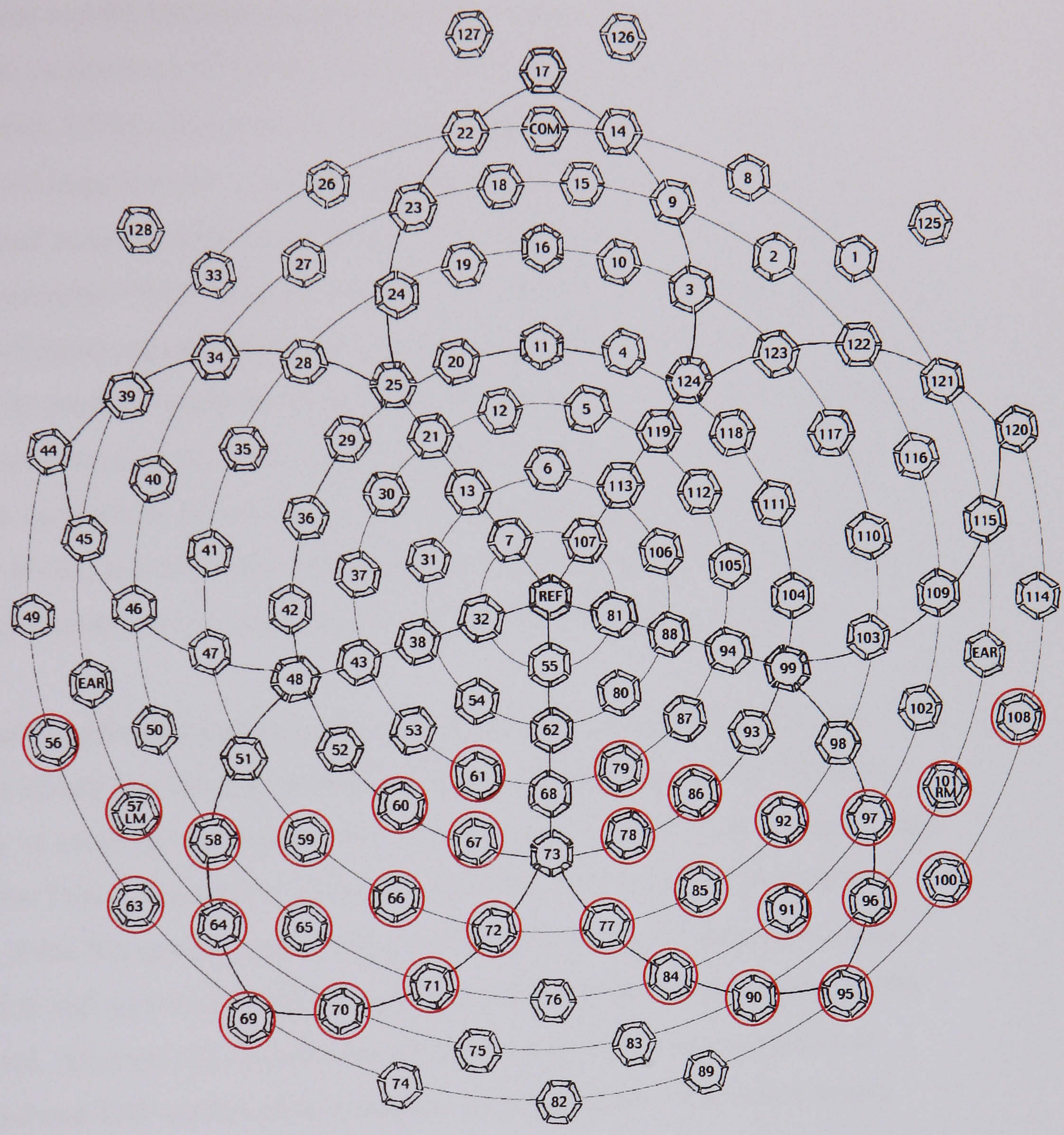


Figure 3.2 128 Channel Scalp Map Showing Analysed Electrode Groups

Alternatively, it is possible to conduct multiple tests if the family-wise (FW) error rate is divided equally amongst the amongst each of the individual tests (e.g. if FW = .05 and four comparisons are made, then each one should be tested at $\alpha = .05/4 = .0125$ (Howell, 1992)). However, this has the disadvantage of increasing the probability of Type II errors. An additional problem is that Analysis of Variance requires equal numbers within each group, and equal variance between groups. A repeated measures ANOVA design may be robust enough to withstand violations of either one of these assumptions but not both (Howell, 1992). All of these requirements present a problem for analysing the results of the current thesis. One solution would have been to test a larger number of participants, and to test equal numbers in each group. However, this was not a practical possibility; Williams Syndrome is rare, and the N for each group represents all usable data from those individuals available at the time that the experiments were being carried out.

An alternative option for analysing the experimental data was to carry out only hypothesis driven statistical tests with a limited number of factors. This offers the possibility of avoiding comparisons between groups of unequal N and variance , and reducing the Type I error due to multiple comparisons by predicting the result of each test. If the WS group response was like that of typically developing controls then the size and nature of the effect, given the same number of participants, could be predicted. Alternatively, hypotheses could be set up on the basis of previous behavioural and ERP studies of WS, and the predicted nature of the abnormality. This was the route chosen. All analyses were carried out to test specific predictions. Amplitude and latency measures for each component were analysed seperately. For experiments in Chapters Four to Six, analyses consisted of a repeated measures ANOVA with Group as a between subjects factor and condition (2 levels) and hemisphere (2 levels, right and left) as within subjects factors. This analysis was then followed up by t-tests to examine specific outcomes. The rationale behind this design was always to compare the results of the experimental group to the matched controls. If the experimental group showed a significant difference to controls then the follow up tests were carried out to confirm what form this difference took.

Where statistical tests were not useful (i.e. due to low number of participants) then visual inspection alone is reported. All analyses of hemispheric lateralisation were carried out on data scaled according to the equation suggested by McCarthy and Wood (McCarthy & Wood, 1985). The alpha for all statistical tests was set at $\alpha = .05$. Where significance is stated to be other than to the .05 level this is to give some indication of the strength of effect (e.g. P<.0001) or trend (e.g. P=.09).

Analysis for the experiments presented in Chapter Seven followed a different format and will be discussed within that chapter.

3.3 Participants

The purpose of the studies in the following chapters was to use the ERP technique to investigate face encoding in Williams Syndrome. However, before doing so a battery of neuropsychological tests, including subtests from the British Ability Scales (BAS) and The British Picture Vocabulary Scale (BPVS), was carried out. These behavioural measures were used first to confirm that each individual conformed to the classic WS cognitive profile of poor visuospatial compared to verbal functioning (Udwin et al., 1987; Bellugi, 1988; Bellugi et al., 2000), and second to give an indication of level of functioning relative to both typical controls (Mental Age), and the other WS individuals.

The ERP paradigm contained no behavioural component for analysis. It was important, then, to have alternative confirmation that the face processing behaviours of the WS group were representative of those documented in the literature. There was good reason to believe that these individuals were indeed typical of the syndrome. All WS adults in the sample had previously been tested on at least one of three behavioural face processing experiments by colleagues at the Neurocognitive Development Unit. These studies all reported the presence of a configural encoding impairment (see Chapter Two). Despite these data, it was felt necessary to confirm that face matching scores were mostly in the normal range, as is commonly reported, for the Benton Test of Facial Recognition. This was the case. The long-form version

of this test was administered to all WS participants in the same session as the other neuropsychological tests , which was on a different day to any of the electrophysiological studies. As can be seen from Table 3.1, the majority of individuals (13/18) were in the normal or borderline normal range for this task. It should also be noted that of those individuals who were classed as 'severely impaired', at least 4/5 had difficulty attending to the task, so these scores are unlikely to be an accurate reflection of true ability. In contrast, all individuals were in the severely impaired range for the Benton Test of Line Orientation, which was used as a non-face matching task comparison. As can be seen from the Table, most people with WS were unable to even pass the pre-test. This pattern is typical of Williams Syndrome (see Chapter Two).

Although the initial aim of the thesis was to test every participant on every experiment, this was not possible in practice. Some individuals were unable to make repeated visits to the laboratory, or were away from the country for a segment of the testing period. In addition, not all data collected were useable. Both of these factors mean that the data sets vary in size for each experiment. However, data presented for all experiments were taken from a subset of the population detailed here.

Experiments were conducted in up to five different sessions for each participant, and no participant in any group took part in any more than two studies in a single day.

3.4 Recruitment and Diagnosis

The individuals contacted to take part in these studies were all those of appropriate ages known to the WS Foundation UK, living in the London and South-East areas. Every individual who had a positive diagnosis and responded in the affirmative was tested. All individuals with WS were encouraged to be FISH tested for ELN deletion. All those that did so received a positive diagnosis. However, three individuals did not wish to undertake the test. Their reasons ranged from needle-phobia to not considering the test relevant to them. All individuals, with and without FISH confirmation, were judged by independent professionals to fulfill diagnostic

criteria for WS, such as the characteristic facial dysmorphology and cognitive profile.

3.5 Summary of WS Neuropsychological Performance

The neuropsychological profiles presented in Table 3.1 are very typical of people with WS. On the recall of designs subtest of the BAS, which involves copying a simple design from memory, 50% of individuals were below floor level. Of the rest, none reached above an MA of 8.9 years, despite chronological ages much higher. The pattern construction subtest, for which participants must arrange coloured blocks into a target pattern, has a lower floor level (2:10 years). Yet two participants were at floor, and most had an MA of around 5 years. In contrast, scores for the BPVS, which is a task in which the individual is required to point to a picture matching a spoken target word, were relatively good. Two participants even scored near to ceiling levels, and most reached a verbal MA of around 8 years. Taken as a whole, these data confirm the typical imbalance between visuospatial and verbal performance in adolescents and adults with Williams Syndrome.

3.6 Typical Control Group

Adolescent controls were children of staff members recruited by e-mail to all employees at the Institute of Child Health and Great Ormond Street Hospital for Children, London. Adult controls were recruited by word of mouth, and by e-mail to all staff members as for adolescent controls. No control had a history of developmental disorder, brain damage, epilepsy, or drug or alcohol abuse. They were assumed to be at normal MA for their CA; no measurements of MA were made independently. They were individually matched on chronological age (+/- 6 months), and sex to the WS group. All participants (in all groups) had normal or corrected to normal vision, on the basis of parental or self report.

3.7 Autism Group

Participants were 8 adults with autistic spectrum disorder recruited from a previous study. All were well within the 'normal range' on global IQ (above 80) on the WAIS-R, and were diagnosed by experienced independent clinicians using DSM-IV criteria. The participants within the autism group were unlike the typical controls in that although mean age across the groups was similar, they were not chosen as individual age 'matches' for the WS adult group. This was due to a practical problem. Ideally individual matches with autism would have been used but the number of individuals available and able to take part in the study was limited.

People with autism typically show a complimentary opposite neuropsychological test profile to that of people with Williams Syndrome. All individuals were tested using the Benton tests of Face Recognition and Line Orientation in order to confirm a relative weakness in face recognition and a relative strength in visuospatial processing in this particular group. The results are consistent with previous literature (Langdell, 1978; Hobson et al., 1988; Tantam et al., 1989; Volkmar et al., 1989; Boucher & Lewis, 1992; Davies et al., 1994; Teunisse & De Gelder, 1994; Boucher et al., 1998; Klin et al., 1999; Schultz et al., 2000) and are presented in Table 3.2. The Table shows that all participants in the autism group scored within the normal range on the visuospatial task. In contrast, scores were poor for the face recognition task, with four individuals scoring in the severely impaired range, three in the borderline range, and only one scoring in the normal range. This confirms the difference in the profile of relative strengths and weaknesses between the WS and autism groups.

Table 3-1 WS Group Participant Information

Participant	Sex	Age (CA) Session 1	Benton Faces	Benton Lines	Recall Design	Pattern Con (MA)	BPVS (MA)	FISH Positive
WS Adoles								
1	F	10.2	36 (Severe)	F	< 5	4:10	7:6	√
2	F	11.2	41 (Normal)	F	< 5	5:4	10:2	√
3	M	12.5	41 (Normal)	F	< 5	2:10	7	√
4	F	12.8	39 (Borderline)	F	< 5	5:1	9:4	√
5	M	13.4	38 (Borderline)	F	5:4	5:7	8:1	√
6	M	14.8	36 (Severe)	Severe	< 5	5:1	7:4	√
7	F	15.5	39 (Borderline)	F	5:4	5:4	8	Untested
8	M	15.6	51 (Normal)	Severe	6:1	5:7	8:7	√
9	M	16.6	41 (Normal)	F	5:7	4:10	9:10	√
WS Adult								
1	F	19.4	29 (Severe)	F	< 5	4:10	4:4	√
2	M	19.8	36 (Severe)	Severe	5:7	5:10	10:2	Untested
3	M	21.7	43 (Normal)	F	< 5	4:10	8.1	√
4	F	21.8	42 (Normal)	F	< 5	3:4	8.4	√
5	F	27.7	41 (Normal)	Severe	5:7	5:4	8	Untested
6	M	30.9	46 (Normal)	F	6:1	7:1	17	√
7	M	34.9	49 (Normal)	F	< 5	2:10	7:6	√
8	F	43.7	42 (Normal)	F	8:9	8:9	17	√
9	M	52.1	35 (Severe)	F	5:9	4:10	16	√

Table 3-2 Autism Group Participant Information

Participant	Sex	Age (CA)	Benton Faces	Benton Lines
1	M	20.3	30(Severe)	25 (Normal)
2	M	21.11	48(Normal)	23 (Normal)
3	M	27.4	35 (Severe)	25 (Normal)
4	F	31.3	35 (Severe)	30 (Normal)
5	M	32.6	40 (Borderline)	30 (Normal)
6	M	32.7	31 (Severe)	30 (Normal)
7	M	35.1	40 (Borderline)	29 (Normal)
8	F	45.4	39 (Borderline)	29 (Normal)

Chapter Four

Human-Face Processing

4 Human-Face Processing

4.1 Experiment One A – The Endstate

4.1.1 Introduction

Chapter One argued for the characterisation of the N170 ERP component as reflecting the 'structural' encoding stage of face perception. As already described, the N170 to face stimuli is a bilateral component that reliably increases in amplitude and latency with face inversion, and is often larger over the right than left hemispheres. The positive peak before the face-specific deflection, the 'P1', is thought to be affected by attention and reflect basic visual processes in V2 to V4. The P2, which is the post-N170 peak, is thought to reflect the first stages of individual face recognition. The entire P1 – N170 – P2 complex occurs within approximately the first 200ms of stimulus processing.

Chapter Two discussed research suggesting that face processing is 'spared' in Williams Syndrome. However, both cognitive and electrophysiological evidence has overturned these claims. Studies investigating behavioural matching of upright versus inverted faces have found a reduced inversion effect for WS compared to controls. This suggests that structural encoding of configural information is atypical in WS. Further cognitive studies directly manipulating face features and configuration have supported this claim. Since face encoding is thought to be reflected in the N170, it could be predicted that this component will reflect the specific encoding difficulties in WS. For example, the N170 may be abnormal in shape or size, and / or abnormally unaffected by inversion.

One study has investigated the electrophysiology of face processing in WS. The principal focus was on late anterior recognition components, rather than the early N170, but the morphology of the first 200ms was found to be 'strikingly different from normal' (Mills et al., 2000). In particular, it was claimed that reduced N100

and enlarged N200 components were found in all WS participants, and that the N200 was larger for those that scored highly on the Benton Face Recognition task. These WS 'marker' deflections are likely to be equivalent to the P1 and P2 components in HD-ERP studies using the average reference. The authors were not able to describe the N170 due to limited recording sites (for further discussion see Chapter Two). While several components and stimulus effects were shown to be right hemisphere lateralised in controls, the WS group displayed absent or left hemisphere lateralisation, although this was always a non-significant trend. These data generate several predictions for a study of the WS N170 to faces: specifically, abnormalities of the early waveform morphology (small P1, large P2) and a lack of right hemisphere lateralisation.

The aim of the present experiment is to conduct a hypothesis-driven investigation of early face perception in the WS endstate. The focus is on the occipito-temporal P1-N170-P2 complex. The hypothesis is that brain development undergoes a subtly different trajectory in developmental disorders such that in WS even good face recognition performance is supported by atypical face encoding. The aim is to investigate whether the WS face encoding abnormality will be evident at the N170.

The predictions to be tested are:

i) Replication: Typical effects in control adults,

ii) Waveform morphology in WS:

Abnormal N170 with reduced P1 and enlarged P2 components,

iii) Stimulus effects: No effect of inversion on N170 amplitude or latency in WS,

iv) Topography: Left hemisphere lateralisation of N170 in WS

4.1.2 Participants

For information on matching and diagnostic criteria see general methods (Chapter Three). Participants were 9 adults with WS, (average chronological age 361 (SD: 138) months), and 9 individually matched typically developing adults (365 (136) months).

4.1.3 Stimuli

The stimuli were the same as those used in (de Haan et al., In press) and consisted of colour pictures of 97 adult female faces each at 12.1 degrees visual angle, from a viewing distance of 75cm. Each face was shown once upright and one inverted for a total of 194 trials. Order of presentation was random with the constraint that the same orientation did not occur for more than three consecutive trials. Each stimulus presentation was for 500ms, followed by an inter-stimulus-interval of approximately 1000ms (+/-200ms) during which time the screen was grey.

4.1.4 Results

Prediction 1A(i): Replication: Typical effects in control adults

N170 results for the typical adult control group replicated those of previous studies. The peak amplitude was larger for inverted (-9.35μv) compared to upright (-7.33μv) faces ($F(1,8)=30.22$, $P<.001$), and the latency was longer (average 147ms; 153ms, $F(1,8)=23.82$, $P<.001$). Inversion effects were visible at the group level and at the level of each individual without exception. There were no significant hemispheric asymmetries. However, topographic amplitude maps (illustrated in fig. 4.9 at the end of this chapter) revealed that the average activity for all participants was slightly more negative over the RH, especially for the inverted face condition. Although non-significant, the direction of this suggestion of lateralisation is at least consistent with previous studies.

Discussion 1A(i)

These results replicate the critical finding in previous studies of significantly later and larger N170 to inverted faces in a typical adult group. They confirm that the effect is extremely consistent across electrodes and participants, such that it is highly significant even in an experiment with a comparatively low sample size (N=9).

Prediction 1A(ii): Waveform morphology in WS: Abnormal N170 with reduced P1 and enlarged P2 components

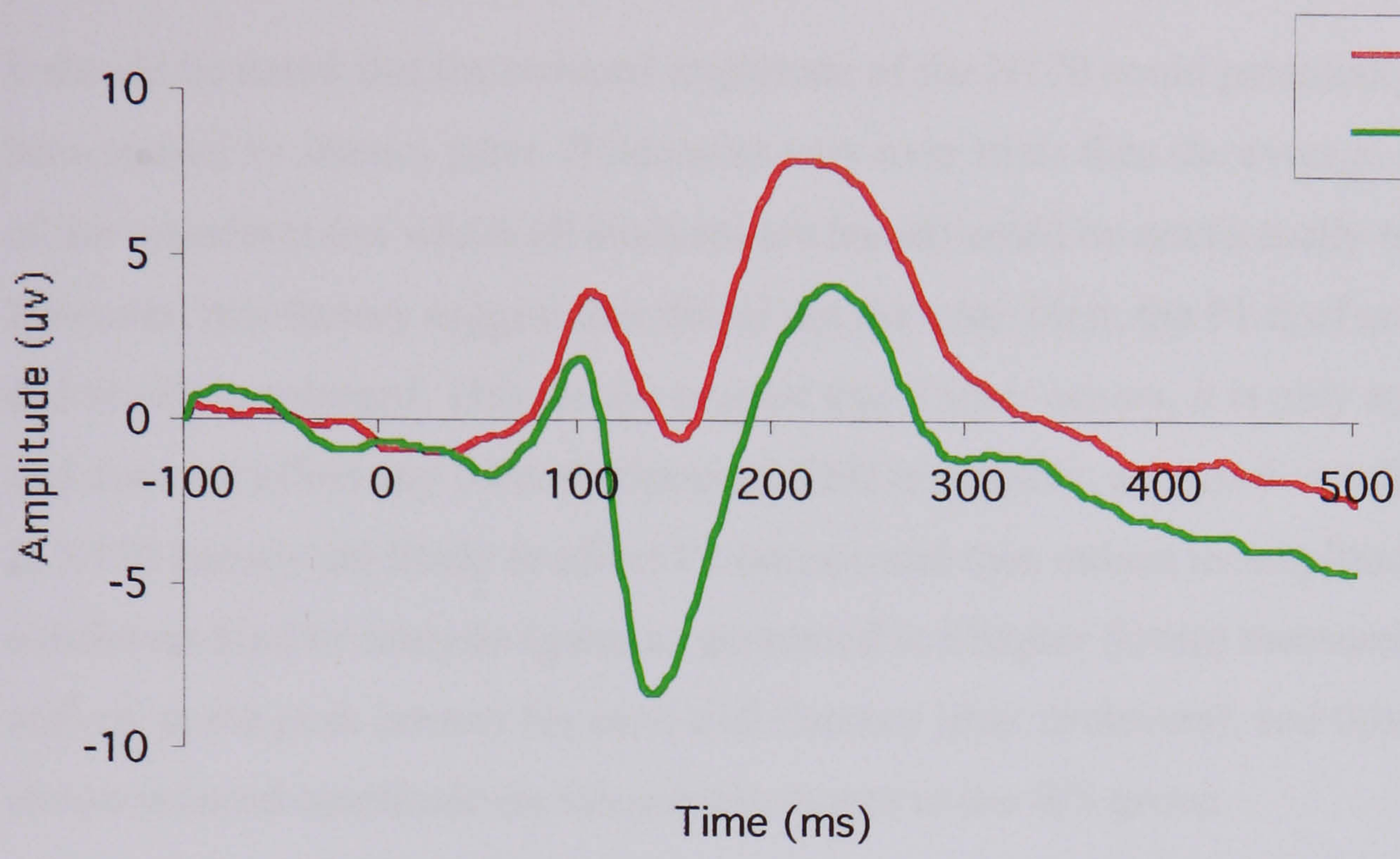


Figure 4.1 Adult group waveform to upright human face (Sensor 91)

All three components of the P1-N170-P2 complex were present in the WS adult waveforms. This is illustrated in Figure 4.1 of the waveform for each group at sensor 91. This electrode was chosen for illustration on the basis that it is where the N170 was maximally elicited for the control group. The amplitude of the P1 was similar to that of the adult control group ($F(1,16)=.08$, P=NS), but the N170 was significantly smaller (WS Mean = -3.76μv, $F(1,16)=11.43$, $P<.005$). Visual inspection suggested a striking amplification of the P2, the mean peak in the WS group (6.03μv) being double the size of that of controls (3.01μv). This was confirmed in the analysis as a trend towards significance ($F(1,16)=3.6$, $P=.076$). However, the amplitude of the P2 relative to the N170 was normal. In other words, there were no significant differences in the P2 when the individual values were adjusted by subtracting the N170 ($F(1,16)=.70$, P=NS). The role of N170 was further supported by peak-peak analysis of the P1 minus the N170. If the N170 was the primary abnormality, as opposed to the component being affected by earlier

processing, then there should be a significant difference between the normal P1 amplitude and the abnormal N170 amplitude in the WS group compared to the adjusted values of the Control group. This is the case ($F(1,16)=8.15$, $P<.05$).

It should be noted that the reduced amplitude of the N170 could potentially have been caused by latency jitter. If latencies vary over trials then the average amplitude of the waveform (on which all analyses are based) could be artefactually reduced. However, two factors suggest that this is not the case. First, the P1 is of normal size and the P2 is enlarged. This would suggest that if jitter occurs, it is only at the N170 and does not affect any other component. This is unlikely, as significant differences in N170 latency are likely to affect P2 latency and thus reduce its amplitude. Finally, a different kind of analysis (gamma, presented in Chapter Seven) measures induced activity at the peak latency for each trial (latency jitter irrelevant), and this also shows reduced amplitude (in the gamma range) in the WS group.

Latencies were not significantly different for the two groups (N170, $F(1,12) = 1.85$, $P = NS$; P2, $F(1,12) = .00$, $P = NS$), except for the P1 latency which peaked significantly later for the WS adults ($F(1,12) =8.13$, $P<.05$).

Discussion 1A(ii)

These results suggest that the morphology of the WS adult waveform to human faces is abnormal. Further, the waveform morphology was not distorted by a reduced P1 or enlarged P2, as would be predicted from the results of Mills et al. (2000). Instead, it was distorted by an abnormally small N170, which supports the hypothesis that structural encoding is poor in the syndrome. From this study it is unclear whether the WS waveform is simply delayed, or whether it develops differently. Throughout typical development, configural encoding increases and, correspondingly, the N170 deflection increases in size. Without WS developmental data, it is impossible to conclude whether the waveform morphology of the endstate represents simply gross delay, or the product of atypical development. This question is addressed in the next experiment (1B). The data from Experiments 1A and 1B will then

be combined to increase the group N, such that correlations can be investigated. This will allow the linear inverse relationship between CA and N170 amplitude to be confirmed for this control group, and to be investigated in the WS group. In addition, it will allow the relationship between MA and N170 amplitude to be investigated in the WS group (equivalency of CA and MA is assumed for control groups).

The delay in peaking of the P1 in the WS group probably reflects a general delay in speed of processing, which might be expected due to low MA. According to this hypothesis, there should be a decrease in P1 latency with increasing age in typical development (thought to be because of increasing absolute processing speed, although processing speed relative to age matched peers may not vary with age), up to a ceiling adult level. Correspondingly, there should be an inverse relationship between MA and P1 latency in WS. This will be investigated by analysing combined data from experiments 1A and 1B. However, even if this correlation is found to be significant, it is unclear why the P1 peak latency would be singularly delayed in WS in the absence of delay of the other components.

Prediction 1A(iii): Stimulus effects:

No effect of inversion on N170 amplitude or latency in WS

There was a main effect of group ($F(1,16)=11.43$, $P<.005$) and a highly significant interaction of group with condition for the N170 amplitude ($F(1,16)=9.51$, $P<.005$). Further analysis revealed that this was because there was no effect of condition for the WS group ($F(1,8)=1.06$,P=NS). This is illustrated in Figure 4.2 which shows peak mean amplitudes for the two conditions for both groups.

In contrast, the latency of the N170 was normally affected by inversion (upright, 155ms; inverted, 164ms), as represented by a main effect of condition ($F(1,16)=21.97$, $P<.001$) and the absence of a group by condition interaction ($F(1,16)=1.69$, P=NS). Visual inspection revealed that the lack of effect on

amplitude was true for all WS individuals, regardless of age and including one participant with IQ in the 'normal range'.

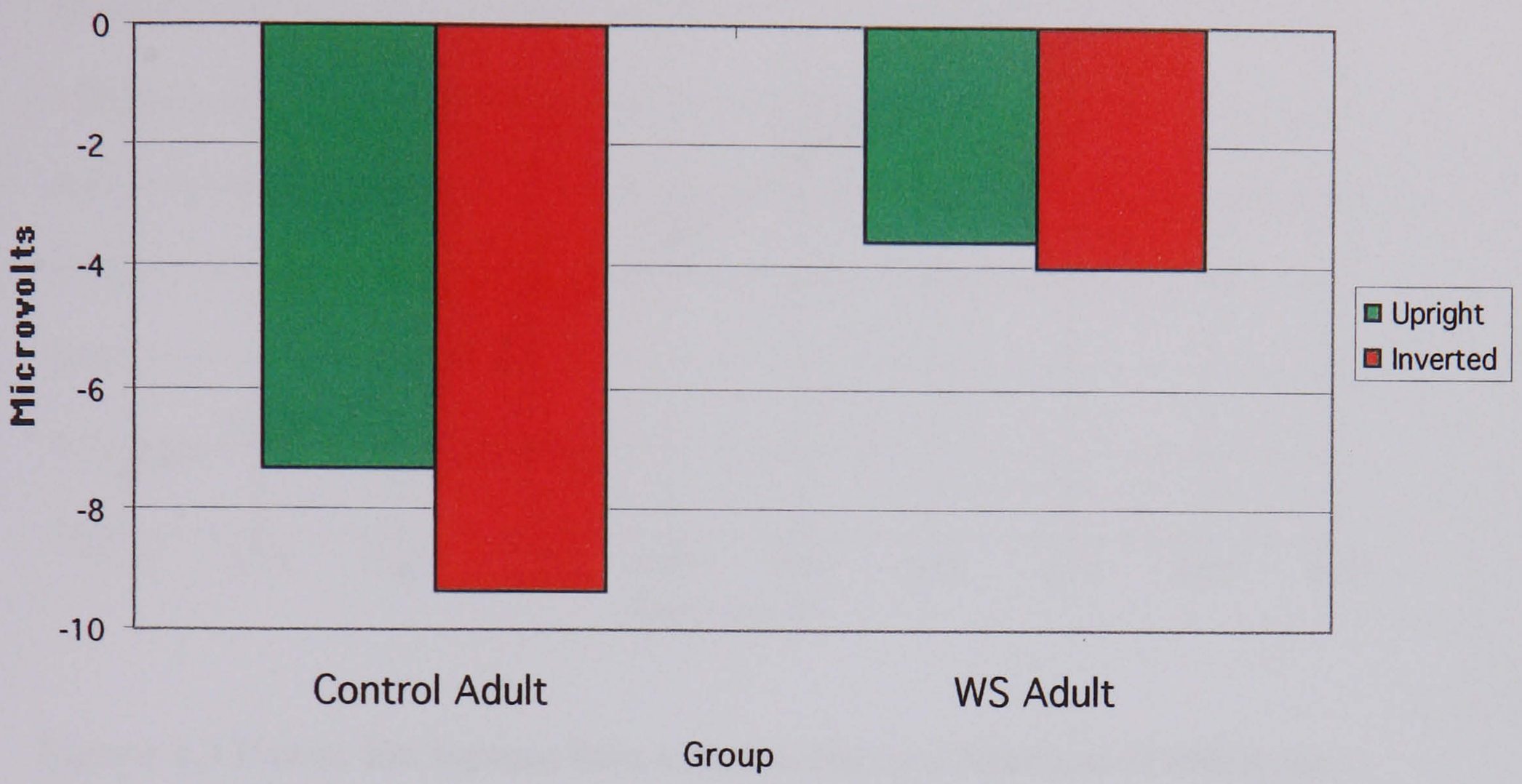


Figure 4.2 Adult N170 amplitude to upright and inverted human face

It should be noted that despite the small number of individuals in each group, the experiment would have had sufficient (medium) power to detect a significant difference between upright and inverted amplitudes, even had the difference been as low as 0.7 μv. This is illustrated in the Figure 4.3 which shows power as a function of effect size, where f = mean difference / SD of mean difference.

Discussion 1A(iii)

Results confirm that there is some abnormality in WS in the treatment of inverted compared to upright faces by 170 ms, even though the latency is normal. As discussed in Chapter One, there are currently several possible explanations for the N170 inversion effect in the typical adult. Amplitude enhancement may be caused by increased neural activity, of the same processor as for upright faces, due to

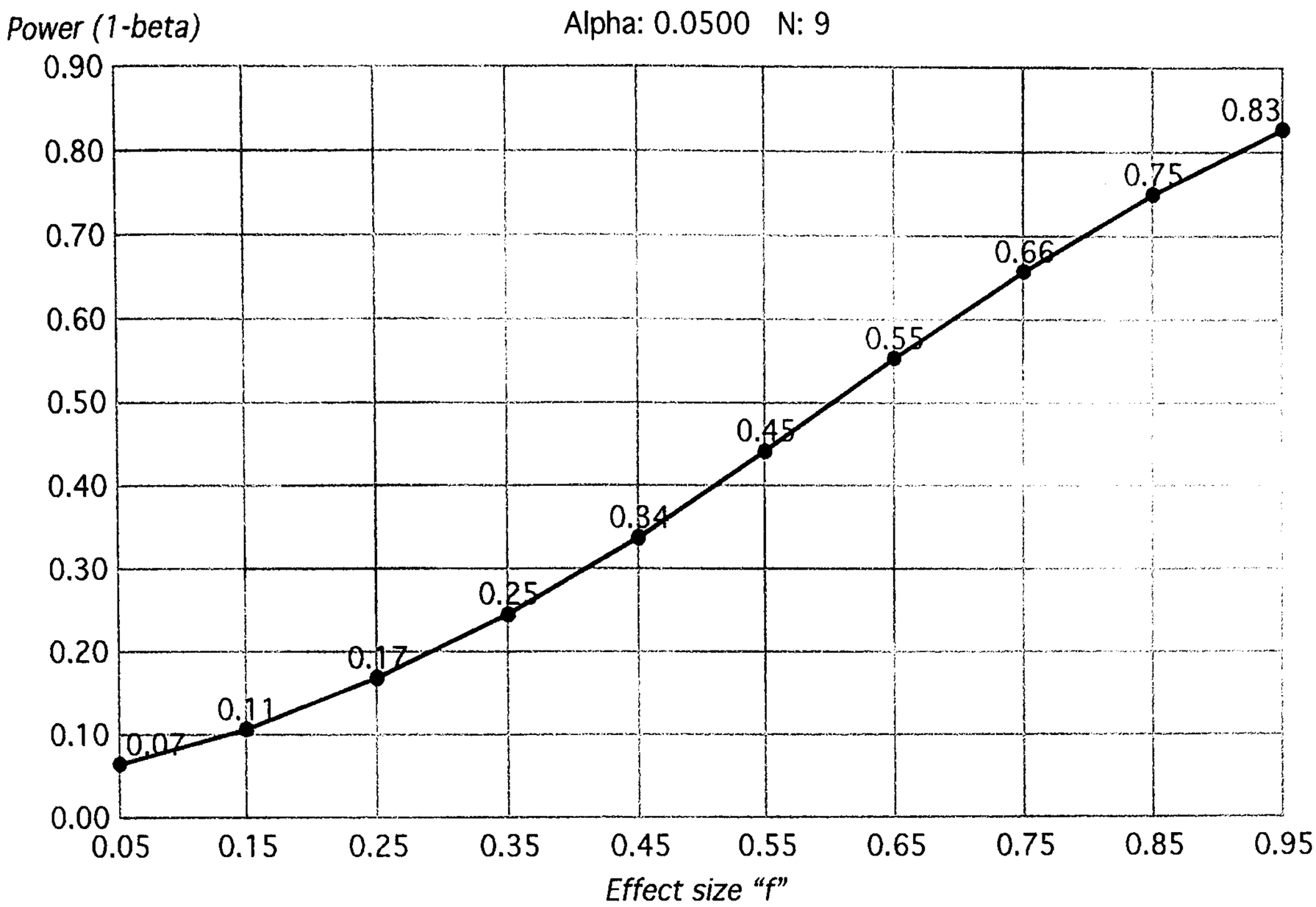


Figure 4.3 Power for human face experiment as a function of effect size

increased encoding difficulty either because the loss of configural information, or a lack of experience with inverted faces, or an interaction of both of these factors.Alternatively, it may be that the inverted face recruits both 'face' and 'object' cortical areas (whereas the upright face just recruits the 'face' area), and the increased amplitude reflects the activity of both. The increase in latency could be due to a decrease in detection / encoding speed. Alternatively, it could be due to the activity of an additional long lasting attentional component, which peaks significantly later than the encoding mechanism, causing summation at the scalp to increase in average latency and amplitude.

One explanation then, of the WS result is that the neural activity for encoding does not vary for upright or inverted faces, but its initiation is delayed by inversion, hence the latency effect. In other words, despite an increase in difficulty of encoding, the activity of the system does not increase in the typical way. There is one published

study on the N170 inversion effect over typical development (Taylor, Edmonds et al., 2001). In this study the effect of inversion on N170 amplitude but not N170 latency increased with increasing age from ten years onwards. This suggests that the lack of inversion effect on amplitude for the WS adult group may represent grossly delayed rather than atypical development. Experiment 1B will address this question.

Prediction 1A(iv): Left Hemisphere Lateralisation of N170 in WS

No statistically significant effect or trend approaching significance was found to suggest hemispheric lateralisation in either group (Main effect of hemisphere, $F(1,16)=.01$, P=NS, interaction with group, $F(1,16)=.43$, P=NS). However, the topographic amplitude maps presented in Figure 4.9 suggest that in contrast to the Control group, who exhibit a slightly larger average amplitude over the RH, the WS group show slightly more LH than RH activation.

Discussion 1A(iv)

The hemispheric prediction was not statistically supported. In addition, the lack of effect was difficult to interpret, due to the lack of effect in the control group. However, topographic maps indicate that there were some differences in the predicted direction. Clearly this observation must be treated with extreme caution. The lack of statistical significance may be due to the low sample size. If the N was increased in both WS and Control groups, then the differences in topography may become significant. Unfortunately, this highlights one of the difficulties with conducting research on such a rare syndrome. However, topography will be further considered in the next experiment, using combined data from adults and adolescents to investigate whether abnormalities can be detected with a larger N.

4.1.5 Discussion

This experiment supports the hypothesis that face processing is atypical in Williams Syndrome. It offers no support to the view that face processing is an 'intact' module. More importantly, it indicates that it is the temporal period in which *encoding* takes place that is most affected, at least using this paradigm. It is the N170 that shows abnormal stimulus effects in terms of amplitude. The structural encoding system is

slowed as in typical adults by an inverted stimulus presentation, indicating difficulty with encoding the inverted stimulus as a face. However, the system does not respond to increased difficulty with increased activity.

Noteworthy is the fact that it is the reduced size of the N170 that causes the impression of the abnormally large P2, predicted on the basis of previous studies. If there is an early electrophysiological 'marker' for WS, it is the N170 rather than the P1 or P2, contrary to previous claims. The WS waveform was not completely abnormal overall. All components were identifiable, there was no significant difference from controls in hemispheric lateralisation, and there was an effect of stimulus inversion on the N170 latency.

In conducting this study it was possible that evidence would be found for completely different electrophysiological correlates of face processing in WS. It was plausible that, with differences in overall brain development, electrical di-poles would be differently oriented to produce alternative or abnormally localised components. This turned out not to be the case. It was the N170 alone that was found to be atypical. However, it would be incorrect to say that the neural processes indexed by the P1 and P2 were 'intact'; rather that this experiment found no evidence of difference. Given what is known of brain development, (see Preamble) it is unlikely that structural encoding would have been affected in isolation from other processing mechanisms. The experiment was designed specifically to highlight abnormalities of encoding. Had the experiment been designed to test recognition, for example, then abnormalities of components later than the N170 are likely to have been found.

Proficiency of coding configural information is thought to develop with experience. Although individuals with WS typically receive high face input, it may be that the quality of this repeated experience is inadequate. For example, 'sticky fixation' may limit the visual scanning of the whole face and narrow the focus to one small area such as the eyes. If configural encoding of faces is poor then it could mean that the WS visual system has failed to specialise for faces over other objects, and simply

processes all visual stimuli in the same way, using the same system. It is equally possible that the endstate processing represents that of a partially specialised rather than fully developed system, i.e., WS face encoding is grossly delayed rather than abnormal per se. One way to address this question is to investigate part of the developmental trajectory.

4.2 Experiment One B - Developmental Trajectory during Adolescence

4.2.1 Introduction

The aim of this experiment was to provide data to support either a 'delay', or an 'atypical trajectory' account of face encoding in WS. An adolescent group of WS was recruited and compared to a group of typically developing controls of the same chronological age. The adolescent age range (10-16 years) was chosen for a number of reasons. The adult WS group results showed an adult-like latency inversion effect but no amplitude effect. This is similar to the result found in a previous study with typically developing adolescents, for whom the latency inversion effect was mature by 10 years of age but the amplitude effect continued to increase until adulthood (Taylor, Edmonds et al., 2001). In other words, the adult WS waveform of Experiment One A looked and behaved more like that of typical adolescents than adults. One hypothesis is, then, that the face encoding of people with WS develops normally through adolescence, but reaches a ceiling of development shortly before adulthood. The only way to test this hypothesis is to compare the waveform of the WS adults with that of typical adolescents and WS adolescents, because all should look and behave in a similar way. Alternatively, if WS face encoding follows an abnormal developmental path, then it should be highlighted by abnormalities of the N170 over adolescence as well as adulthood. In this case, the WS adolescent waveform may be different to that of the typical group, with differences corresponding to those between the WS and typical adult groups. This was the experimental hypothesis. It generated a number of specific predictions for the WS group compared to the typical group:

i) WS Morphology: Abnormal waveform with small N170,

ii) WS Morphology: Small N170 causing P2 amplification,

iii) WS Stimulus effects: No effect of inversion of N170 amplitude,

iv) WS Topography: Left hemisphere lateralisation of N170.

In addition, four other predictions were made of the data when combined with that from the previous study

v) Negative correlation between age and N170 amplitude across groups,

vi) No correlation between neuropsychological test performance and N170 amplitude in the WS group,

vii) Higher face recognition behavioural scores associated with larger P2 amplitude,

viii) Negative correlation between MA and P1 latency in WS group, and CA and P1 latency in control group.

4.2.2 Participants and Stimuli

Participants were 8 individuals with WS, average age 158 months (SD: 24), and 8 TD adolescents, average age 158 months (23). Stimuli and procedure were the same as those for the previous experiment.

4.2.3 Results

Prediction 1B(i): Abnormal waveform with small N170

The waveform displayed by the WS adolescents looked different from that seen in the other groups, see Fig. 4.4. Positive and negative deflection components could still be identified, but the N170 equivalent deflection was very obviously smaller than that of controls ($F(1,12)=11.2$, $P<.001$). It was also positive rather than negative in value. In contrast, the P2 value was much larger in the WS group ($F(1,12)=13.16$, $P<.005$). The amplitude of the P1 was very similar for both WS and control adolescents ($F(1,12)=.08$, P=NS).Latencies were not significantly different for the WS group compared to controls (P1, $F(1,12) =.02$; N170, $F(1,12) = 2.94$; P2, $F(1,12) =.01$).

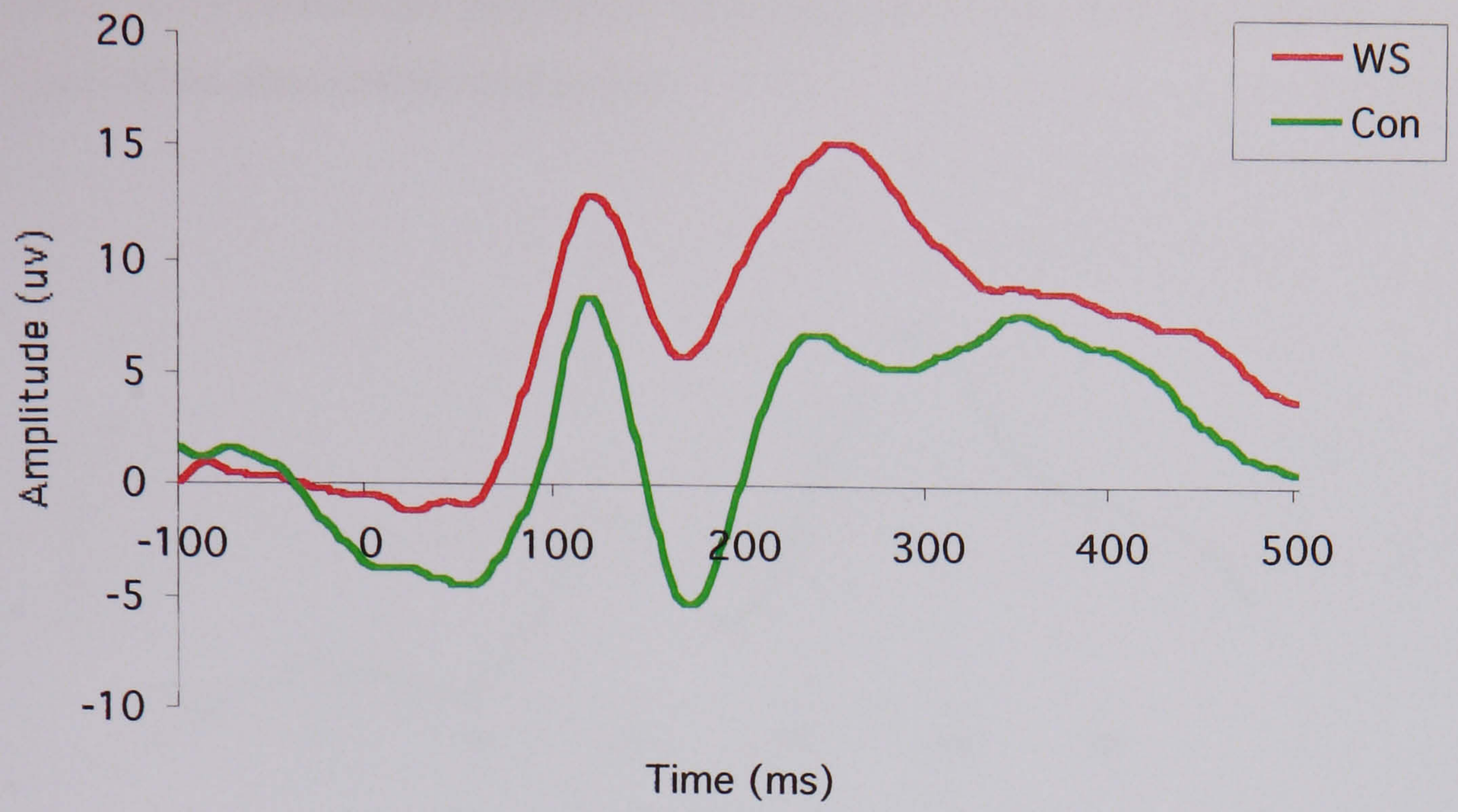


Figure 4.4 Adolescent Group Waveform to Upright Human Face (Sensor 91)

Discussion 1B(i)

Waveform morphology for WS adolescents was abnormal compared to CA controls. The positive value of the N170, and the large P2, gave the appearance of a waveform like that of typical young infants (Figure 4.5 from de Haan et al., In press). However, latencies were not infant-like but equivalent to those of the controls. It is N170 amplitude, and the absolute amplitude of the P2, that differentiates WS adolescents from typically developing adolescents.

There are some striking similarities between the abnormalities of theWS adult and WS adolescent waveform morphologies. This is despite the differences in the initial appearance of the waveforms. There is no evidence from these data that face encoding in WS develops typically at any stage. The amplitude (as well as the latency) of the WS adolescent P1 was no different from that of control adolescents ($F(1,12)=.08$, P=NS). This suggests that at least basic visual processes function relatively normally using this paradigm, and that the N170 is the first visual processing component to be severely affected in WS. This is not to say that attention and V2 to V4 are normal in WS! But in this paradigm, using these stimuli, low level

visual abnormalities and attentional differences during the task are unlikely to be the cause of the abnormalities observed.

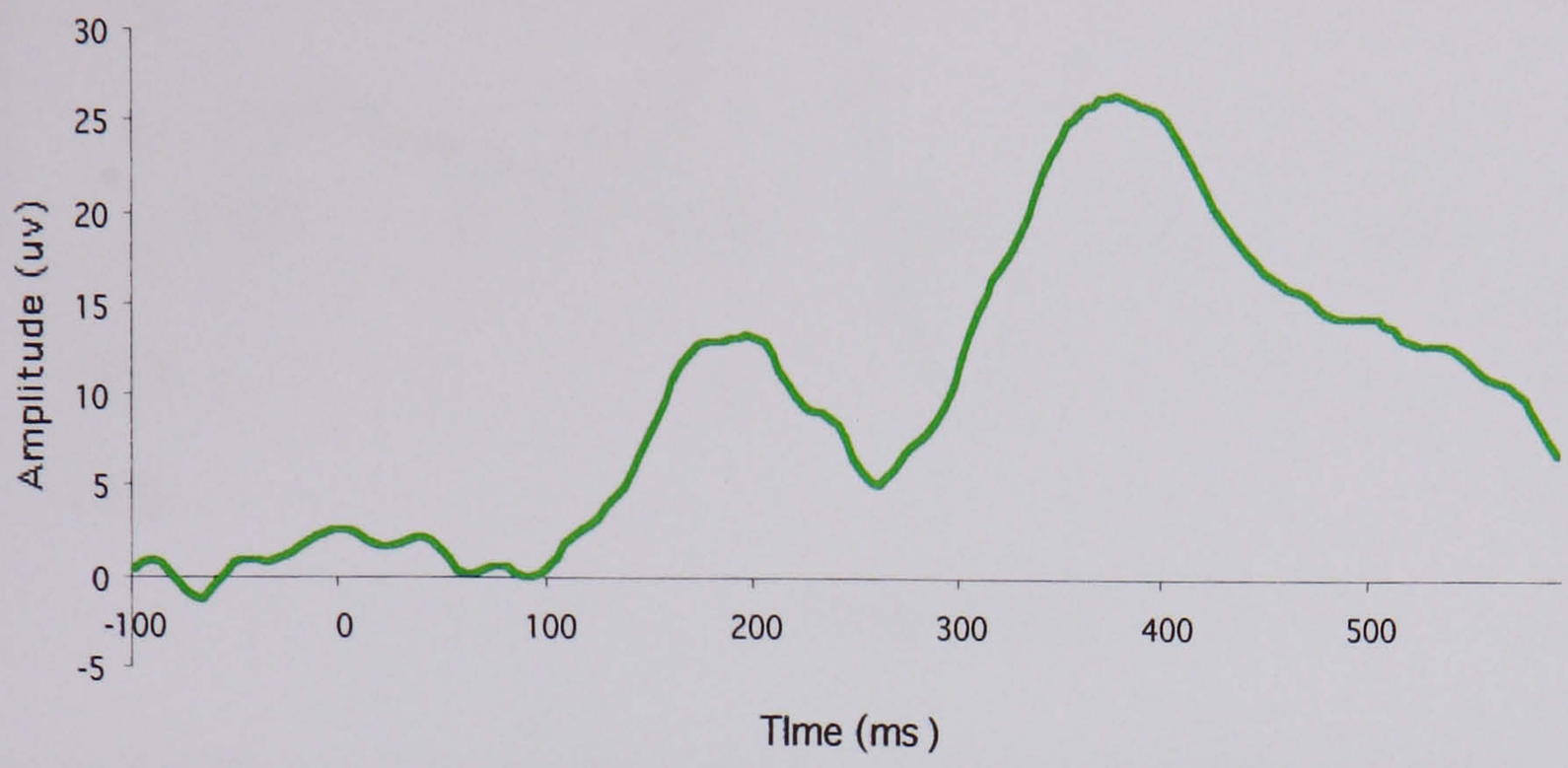


Figure 4.5 Infant Waveform to Upright Human Face (from de Haan et al.,. In press)

The WS adolescent waveform was different from that of age-matched controls, and did not match that of any group tested by Taylor et al. (Taylor et al., 1999). However, in order to ensure that the WS adolescent group weren't displaying a delayed waveform, an additional group of 8 typically developing children aged 6-7 years was tested. This age group roughly corresponds to the global MA of the adolescent WS group. Figure 4.6 shows a waveform from 5 subjects (3 discarded due to insufficient trials). There were insufficient numbers for statistical analysis, but the waveform is visibly different to that of the WS adolescent group. In particular, the N170 is a large deflection that reaches negative values for the upright face, and latencies are delayed compared to the WS group. These data provide no evidence to support a delay hypothesis.

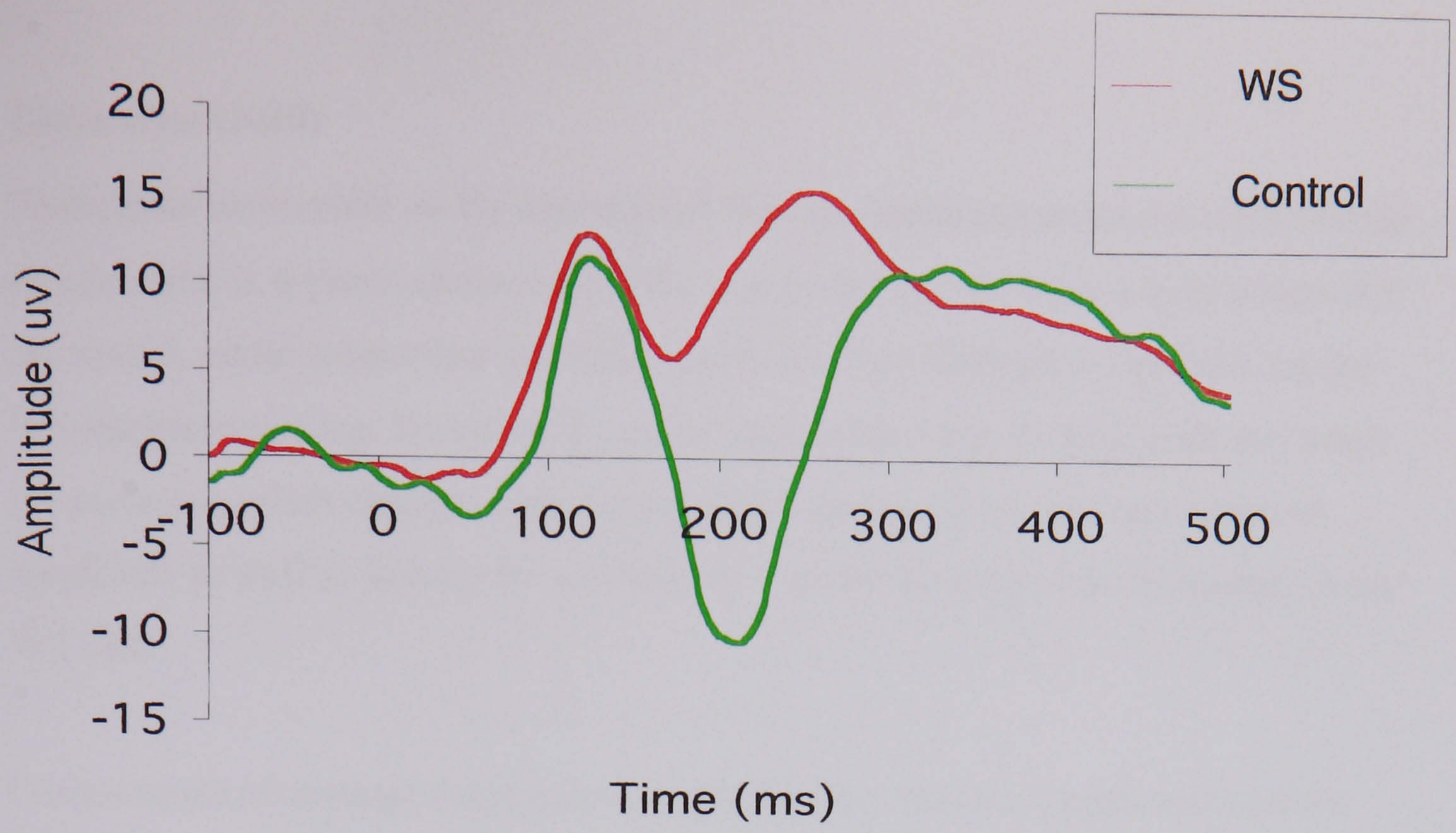


Figure 4.6 Typical Child Waveform Compared to WS Adolescent Waveform (Sensor 91): Upright Human Face Stimulus

Prediction 1B(ii): Small N170 causing P2 amplification

When the P2 was adjusted to take account of the N170 there was no significant difference between groups ($F(1,12)=.02$, P=NS). In contrast, the P1 minus the N170 was significantly different ($F(1,12)=4.61$, $P<.05$) between groups.

Discussion 1B(ii)

The abnormality in morphology confirms the prediction and clearly mirrors that found in the adult WS group. This supports the finding in the adult group and refutes the claim of (Mills et al., 2000) that it is the P2 equivalent which is abnormal in the disorder. The fact that the N170 is again implicated also suggests that Williams Syndrome most affects structural encoding compared to other early components of processing. However, it is unclear whether this abnormality is face specific. This will be investigated in the following chapters.

Prediction 1B(iii): No effect of inversion of N170 amplitude

Inversion of the face stimulus made no significant difference to N170 amplitude in either of the adolescent groups (Main effect, $F(1,12)=1.32$; Interaction, $F(1,12)=.03$), although latency was normally delayed in both ($F(1,12)=4.75$, $P<.05$).

Discussion 1B(iii)

Predictions were made on the assumption that the amplitude inversion effect would be adult-like in typical adolescents. This was in fact not the case, which means that the results, while supporting the initial prediction, are difficult to interpret for the WS adolescent group. However, it can be said on the basis of these data that while the inversion effect changes over typical development (in becoming evident in amplitude as well as latency by adulthood), it shows no sign of development in the WS case.

Comparisons of average amplitude data for the face-specific component and the following P2 of WS adult compared to TD controls could tentatively support a delayed development hypothesis (the WS adult amplitude is very similar to that of the TD adolescents for the N170 and P2 components). This was not true of the P1, which may be because it is a component thought to reflect general visual processes rather than face-specific processes (average P1 amplitudes for both WS groups were identical to what would be expected for their chronological age, see fig. 4.7). It was also untrue of latency (see fig. 4.8) for which the N170 and P2 were similar to chronological age, and the P1 was very similar to TD adolescents. Conclusions from such comparisons are limited, as WS adult and TD adolescent groups were unmatched on any possible measure (e.g. Mental Age). However, inconsistency between 'delayed' amplitude and 'normal' latency across age argues more for atypical than delayed processing.

Prediction 1B(iv): Left hemisphere lateralisation of N170

There was no main effect of hemisphere for the amplitude or latency of N170 ($F(1,16)=.01$; $F(1,16)=.30$, P=NS),or interaction of hemisphere with group ($F(1,16)=.43$; $F(1,16)=.43$, P=NS). However, scalp maps indicate that the control adolescent group N170 was RH lateralised, while the WS N170 was bilateral or LH lateralised.

Discussion 1B(iv)

The prediction was not supported. There was no significant effect of lateralisation of N170 in either adolescent group. This may be a result of low sample size. In order to confirm whether the apparent lack of lateralisaton was due to the low N in each group, age groups were combined from experiments 1A and 1B, and hemispheric data reanalysed. This analysis yielded a main effect of group as would be expected ($F(1,30)=12.34$, $P<.001$), and a significant interaction of group with hemisphere ($F(1,30)=4.96$, $P<.05$). The interaction was because, as predicted, the WS group N170 was larger in amplitude on the left compared to the right (trend, $t(15) = 1.57$, $P =.07$) and the control N170 was larger on the right compared to the left (trend, $t(15)=1.60$, $P=.06$). Normalised data (McCarthy & Wood, 1985) confirmed the significant interaction ($F(1,30)=4.45$, $P<.05$).

The two cerebral hemispheres are thought to undertake different kinds of visual processing. The LH carries out more featural or analytical processing, and the RH more configural or holistic processing. As discussed in Chapter One, this is thought to be due to the faster maturation of the right hemisphere at a time when infants can only see low spatial frequencies and cannot carry out analytical processing. Face processing becomes more lateralised to the RH with increasing age, and this is often reflected by an increased N170 in the RH compared to the LH. However, the WS RH turns out not to be specialised for faces in the typical way. This may relate to a higher reliance on featural as opposed to configural processing. In other words, faces may be processed in WS using similar systems to those that typical individuals use to process objects.

Prediction 1B(v): Negative correlation between age and N170 amplitude

There was a significant negative correlation between age and N170 average amplitude for both groups when adolescent and adult data were combined (WS, -.65; Control, -.53 ($P<.05$)).

Discussion 1B(v)

In both the WS and Control groups, the N170 deflection increases in size (becomes more negative) with increasing age. This confirms that despite the abnormally small N170 deflection in the WS group, the component does undergo some change and does not reach an abnormal early ceiling. The WS N170 deflection, despite other atypicalities, is 'typical' in the sense that it continues to mature even throughout adulthood.

Prediction 1B(vi): No correlation between neuropsychological test performance and N170 amplitude in the WS group

Raw scores (score calculations unadjusted for age) of Recall of designs (-.3210, P=NS), and Pattern Construction subtests of the BAS (-.0796, P=NS) were used to correlate with the average N170 amplitude in the WS group. In addition, a global measure of cognitive ability in relation to typical development, the General Cognitive Ability (GCA), was used (-.2969, P=NS). No correlation reached significance, even before Bonferroni correction for multiple comparisons.

Discussion 1B(vi)

A correlation between the N170 deflection and cognitive measures should be assumed in the typical group, because standardised cognitive measures should (by definition) be roughly in line with chronological age (which was found to be significantly correlated). This is not the case for the WS group, where scores on cognitive tasks are not significantly correlated with chronological age. However, the prediction is that it is length of experience (CA) rather than relative speed of processing which should affect WS face encoding. It should be remembered that despite other processing problems, face processing in behavioural tasks is not impaired or delayed in WS, but is at age appropriate levels. So the processing style used by people with WS, although atypical, is a successful one. In other words, the lack of correlation between relative cognitive task success and face encoding is not a surprising one. It is chronological age, or 'length of experience', rather than mental age that is related to the N170 amplitude.

Prediction 1B(vii): Higher face recognition behavioural scores associated with larger P2 amplitude

The WS group was divided into 'High' and 'Low' subgroups according to Benton face recognition score. High was classed as scores within the normal range (>41/54), and Low as any scores below normal range (<41/54). Analysis was conducted to see if the P2 amplitude was larger for the high compared to the low group. The analysis confirmed the prediction with a trend ($F(1,15)=3.5$, $P=.08$), similar to that reported by (Mills et al., 2000). This was because the P2 amplitude for the high group (n=9, Mean = 9.89μv) was larger than that for the low group (n=7, Mean = 6.13μv).

Discussion 1B(vii)

The results support those of (Mills et al., 2000) for their WS group. Normal range scores on the Benton face recognition test are associated with increased P2 amplitude. In one sense this relationship is surprising, because it means that those WS individuals who display a P2 which is more similar in amplitude to that of controls, are performing worse than those for whom the P2 looks more dissimilar. This may be an example of the abnormalities of the underlying WS system. Only those individuals whose neural systems are over-active, perform at normal levels. The P2 in typical development is thought to reflect recognition rather than encoding stages of face processing. These data support this view. However, the overt relationship between brain imaging of face recognition and performance on standardised tasks of this type has never, to my knowledge, been investigated in the typically developing population. A study of this relationship should be undertaken before further conclusions can be drawn about the WS group.

Prediction 1B(viii): Negative correlation between MA and P1 latency in WS group, and CA and P1 latency in control group

There was a significant negative correlation between chronological age and the P1 latency in the control group (-.62, $P<.005$). In contrast, there was no such correlation for the WS group (-.24, P=NS). In addition, there was no correlation between any test score and chronological age, even before Bonferroni correction. The variables

were pattern construction MA (sub-section of the BAS, -.13, P=NS), BPVS MA (-.11, P=NS), and scores from the Benton face recognition test (-.23, P=NS).

Discussion 1B(viii)

This analysis highlights the difficulty of choosing an appropriate behavioural measure to correlate with the electrophysiological one. Ideally a measure of 'processing speed' or some measure of attention should have been used. However, such data were unavailable. The measures that were chosen are thought to give either an overestimate (BPVS) or underestimate (Pattern Construction) of real WS MA. However, only these tasks are standardised over the required age range such that the true spread in the WS group can be seen. For example, Pattern Construction is the only spatial or non-veral subtest to have age norms going down to the age of 2 years. On the other tasks, at least 12 of the WS participants are simply at floor (age 4:10 years), which limits the variance necessary for correlational analysis. However, the link between CA and the P1 latency in the control group indicates that brain maturation (probably controlling speed of basic visual processes in V2 to V4) and / or absolute processing speed contribute to the decrease of P1 latency with age.

4.2.4 Discussion

Analysis of data from this experiment reveals similarities and differences of WS development compared to typical development. The N170 is typical in increasing in amplitude with age (for both upright and inverted faces), and is also typical in increasing in latency to inverted faces across age. However, the morphology of the first 200ms of face processing in WS follows an atypical trajectory, and N170 topography is atypical across development. The effect of inversion on the amplitude of the N170 does not change from adolescence to adulthood in WS as it does for controls. In addition, the N170 is small across development causing the P2 component to reach higher values.

It is unclear whether the abnormalities observed to faces in WS are specific to face processing or reflect general differences in visual processing ERPs. This question

will be tackled in experiments two to four. It is also unclear whether the abnormality in the endstate is syndrome specific. This question is the focus of the next experiment.

4.3 Experiment 1C - Syndrome Comparison

4.3.1 Introduction

People with WS may share the face encoding abnormalities revealed in the last two experiments with other developmental disorders. For example, autism is a disorder in which face processing is usually very poor, unlike that of WS which is usually relatively good. People with autism, like those with WS, have been found to show a reduced or absent face inversion effect and to be impaired on tasks requiring configural processing (Langdell, 1978; Hobson et al., 1988; Tantam et al., 1989; Volkmar et al., 1989; Boucher & Lewis, 1992; Davies et al., 1994; Teunisse & De Gelder, 1994; Boucher et al., 1998; Klin et al., 1999; Schultz et al., 2000). A featural processing style, or weak 'central coherence', has been to used explain this poor performance (Frith, 1989). However, the same hypothesis has been used to explain the *good* behavioural performance of people with WS on face recognition tasks. Clearly both accounts cannot be correct in their current form. A broadly defined deficit in configural processing cannot be used to explain both successful and unsuccessful behavioural performances.

The hypothesis of the current study is that people with WS encode faces more on the basis of features than on configuration. This is a deficit hypothesised to be specific to WS, because no other disorder has been documented with good performance supported by such atypical early processing. People with autism, like people with WS, often show a featural bias on tests like the hierarchical figures test in which, for example, a large 'H' is made up of small 'S's (Bellugi et al., 1992; Plaisted, Swettenham & Rees, 1999). In other words, if asked to copy or match the figures, they are likely to do so on the basis of the local elements rather than the global arrangement. However, it was recently demonstrated that when overtly instructed to

attend to the global figure, the performance of individuals with autism was not significantly impaired (Plaisted et al., 1999). This suggests that local processing in autism is a default preference which can be over-ridden by focused attention. The comparison between WS and autism will be discussed further in Chapter Seven. Here it is sufficient to hypothesise that people with autism should be different to those with WS at the N170 configural encoding level (i.e., the autism group N170 should look like that of controls). Other differences between the autism and control groups may implicate abnormalities in attention and early visual processing (i.e. the P1 which was of normal size in the WS group) but not structural encoding. The predictions to be tested are:

i) Waveform morphology: Autism group N170 and P2 but not P1 significantly different from WS adult group (P1 but not N170 and P2 significantly different from Control adult group)

ii) Inversion Effects: Autism group normal amplitude and latency inversion effect (significantly different from WS but not from Control adult group)

4.3.2 Participants and Stimuli

Participants were 8 adults with autistic spectrum disorder (369 (138) months) recruited from a previous study about memory in autism. They were group matched to the WS adults on the basis of chronological age. All were diagnosed by independent external clinicians and satisfied DSM-IVcriteria for Autism or Aspergers Syndrome. Stimuli were the same as those used in experiments 1A and 1B.

4.3.3 Results

Prediction 1C(i): Autism group N170 and P2 but not P1 significantly different from WS adult group (P1 but not N170 and P2 significantly different from Control adult group)

The P1-N170-P2 complex appeared normal. The P1 was of normal size ($F(1,14)=1.42$, P=NS) but the latency to peak took significantly longer in the autism

group compared to both the TD (F(1,14)= 28.17, P<.005) and WS (F(1,14)=11.80, P<.005) adult groups. The N170 and P2 amplitudes were no different from TD adults (F(1,14)=2.40; F(1,14)=1.69, P=NS) and, as a consequence, were significantly different from the WS group (F(1,14)=5.93, P<.05; F(1,14)=6.52, P<.05). There were no group effects on the N170 latencies (TD, F(1,14)=3.34; WS, F(1,14)=.22, P=NS) or P2 (TD, F(1,14)=3.29; WS, F(1,14)=2.61, P=NS). Figures 4.7 and 4.8 provide a graphical summary of the differences and similarities for the autism group compared to all other groups for the P1-N170-P2 amplitudes and latencies.

Figure 4.7 Upright Human Face: Average Amplitude of All Components and Participants

Figure 4.8 Upright Human Face: Average Latency of All Components and Participants

Discussion 1C(i)

The prediction was supported, in that the autism waveform morphology was very different from that of the WS adult group. It is the specific differences, however, that are particularly informative. The latency of the P1 component, which is thought to basic general visual processes and attention, was severely delayed in the autism group. The face-specific N170, which was atypical in the WS case, was normal in the autism case compared to adult controls. Two conclusions can be drawn from these results. First, early perception of faces in WS is different from that in autism, and does not reflect any similarity at the behavioural level. Second, the face processing impairment in autism may reflect general abnormality or delay in visual processing and/or attention, rather than differences in the configural processing of faces per se.

Prediction 1C(ii): Autism group normal amplitude and latency inversion effect (significantly different from WS but not from Control adult group)

There was a small effect on the N170 amplitude, which was highlighted in a group by condition interaction ($F(1,23)=7.45$, $P<.05$) when compared to controls and WS adults, because the difference in amplitude between conditions for the autism group ($t(7)=2.19$, $P<.05$ one way) was smaller than that of the control group ($t(7)=7.85$, $P<.001$), but larger that that of the WS group who showed no differences ($t(7)=1.03$, P=NS). In contrast, there was a main effect of condition for latency data ($F(1,23)=7.81$, $P<.05$), but this did not vary significantly by group ($F(1,23)=1.97$, P=NS).

Discussion 1C(ii)

These data reveal a dissociation between two developmental disorders at the early perceptual processing level, indicating that WS but not autism impairs the structural processing of faces. Individuals with autism displayed an unimpaired waveform which was different only in being slow to onset. Noteworthy is the fact that the purported similarities at the cognitive processing level are underpinned by different processing mechanisms at the electro-cortical level.

4.4 Chapter Four Summary

The event-related potential technique can be usefully employed to investigate aspects of processing in developmental disorders that are unachievable using other techniques. Behavioural studies had previously shown that configural processing of faces is poor in Williams Syndrome. They had not been able to elucidate where in the stream processing was affected, or whether the processing reflected a case of delay or of atypical development. In contrast, the current studies found that the configural impairment was evident as early as the encoding stage of processing, and that face encoding is not merely delayed in WS development, but actually develops differently. In addition, the final experiment confirms that the WS abnormalities are likely to be syndrome specific, at least in as much as they differ dramatically from another developmental disorder which is reported to share the same cognitive

processing 'style'. The reduced size of the N170 is a candidate 'marker' component for Williams Syndrome.

Before drawing any broader conclusions about the nature of WS face encoding, it is necessary to investigate whether the abnormalities of processing present for faces are also present when processing other visual stimuli. This is addressed in the next set of experiments.

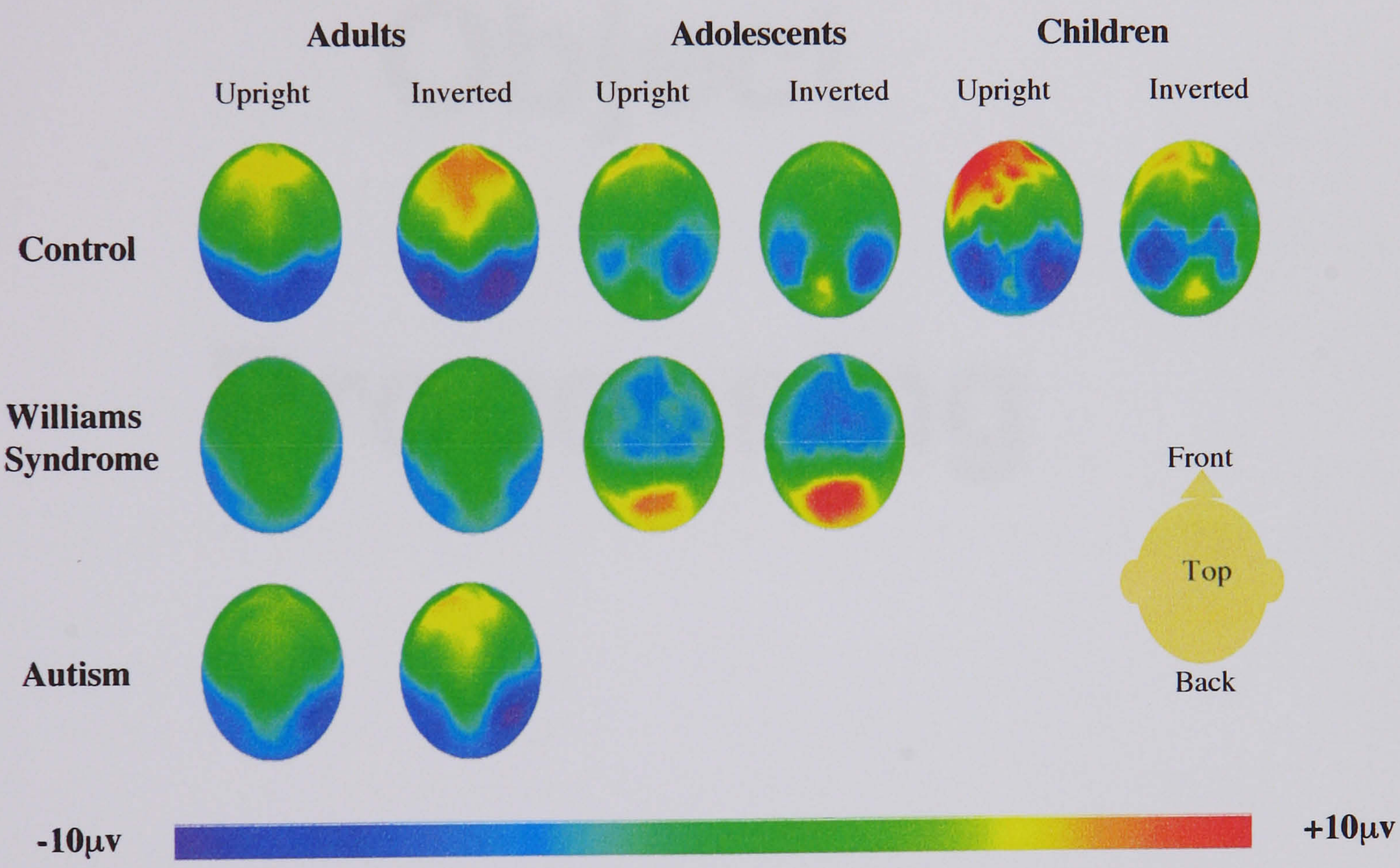


Figure 4.9 Topographic Scalp Maps: N170 peak to Human Face Stimuli

Chapter Five

Object Processing

5 Object Processing

5.1 Experiment Two A - The Endstate

5.1.1 Introduction

Experiments 1A and 1B suggested that Williams Syndrome leads to atypical development of the cortical processes supporting the structural encoding of faces. However, the experiments were unable reveal whether the abnormality is specific to faces. The atypical waveform and stimulus effects found may be general to visual processing in WS, rather than specific to face encoding per se.

Studies of typical adults and typically developing children have shown that N170 is larger to faces compared to other stimuli. This is true even of those stimuli which can also be identified at the level of the individual exemplar, like cars and houses. In addition, N170 shows the inversion effects of increased amplitude and latency only to faces, and not to other object stimuli. For example, upright compared to inverted cars typically elicit no N170 differences (see Chapter One).

There is some reason to believe that the WS abnormalities present in response to faces may not hold for other stimuli. Mills et al. (Mills et al., 2000) discuss 'preliminary' visual inspection of WS adult waveforms to cars, and compare them to previously obtained waveforms to faces. They note differences (N200 is smaller to cars), and topographic distribution changes. This points to some stimulus specificity of the WS electrocortical response. It also suggests that it is the N170 that is implicated, since Experiments 1A and 1B of the current thesis demonstrated that the P2 (equivalent to N200) enlargement could be explained as an artefact of the diminished N170. In short, the 'car' results of Mills et al. in combination with those of the human-face processing experiments of the current thesis, indicate that the WS N170 may be somewhat face sensitive. Unfortunately, however, the method used to obtain the car results is not presented. Stimulus features, such as size and colour, can

have a significant effect on component amplitudes (Rugg & Coles, 1995), yet these are very difficult to control when comparing faces and cars (see Experiment Three below). It is not clear from Mills *et al*. whether these factors were comparable across stimuli, or if the participants taking part in the 'car' experiment were comparable in age to those tested with face stimuli. In addition, the authors present no descriptive data (such as mean amplitudes) or statistical analysis to confirm their visual inspection.

An additional way to investigate stimulus specificity, rather than comparing faces directly with objects, is to investigate the inversion effect. If visual processing in WS is similar for all stimuli, then there should be an effect of object inversion on latency, since this is what is found with face inversion. This effect should be different from that of typical adults who, as already mentioned, have been found to show no inversion effect in latency or amplitude to stimuli other than faces. In contrast, if faces are a special class of visual stimuli to people with WS, as they are to typical adults, then there should be no change in latency (or amplitude) with the inversion of non-face objects. This technique overcomes the requirement to control object and face stimuli for low-level visual features. It does, however, target a slightly different question. If objects and faces are compared directly, then inferences can be made about the underlying systems. Amplitude and latency differences to the two different stimuli, in the absence of topographic differences, would implicate the same system active to differing degrees. The finding of topographic differences would implicate different systems. In contrast, an investigation of the effects of object stimulus inversion can reveal similarities or differences in *processing*. Different *systems* may or may not be active in response to objects versus faces, but they may treat both stimuli in the same way. For example, it may be that the WS N170 to upright cars is topographically different, and at different amplitude and latency to that to faces, but that the processing carried out is similar in that latency is equally affected by inversion.

There are three main questions to ask of the WS electrocortical response to faces compared to other objects. First, are the waveforms similarly atypical compared to controls, in showing a small N170? Second, is the latency of the object N170 affected by inversion? Third, is the N170 different in amplitude, latency or topography? The first two of these questions are addressed by the following experiment in which individuals with WS were presented with upright and inverted car stimuli. Ideally the study would have also included upright and inverted face stimuli for direct comparison. However, this would have required a long testing session with at least 360 trials (90 per condition) in order to get useful data from each participant. This was judged to be unacceptable for the individuals being tested (see general methods). Instead, the direct comparison of car and face waveforms will be made separately in Experiment Three.

Analysis of experiment 2A was guided by three predictions:
i) Waveform morphology: WS group no significant difference from controls (N170, and therefore P2, equivalent to controls),
ii) Stimulus effects: No effect of latency in WS or control groups (cars processed differently to faces),
iii) Topography: No lateralisation, WS group no significant difference from controls.

5.1.2 Participants

Participants were 9 adults with WS. Of these individuals, 7 (CA; 354 (137) months) yielded usable data (loss due to excessive movement artefacts) and were individually matched to typically developing adults (CA; 356 (136)) months.

5.1.3 Stimuli

Stimuli consisted of 25 colour pictures of cars (viewed side on, facing to the left), standardised for size (in pixels) against a plain grey background. Cars were randomly presented at 6.9 degrees vertical visual angle (viewing distance 75cm) a total of 200 times with 50% of the stimuli in the inverted position. Car pictures were sourced from one internet site (www.carpictures.com), and were standardised using the

Adobe Photoshop package. Presentation was for 500ms, preceded by a baseline period (of a small white fixation square) of approximately 300ms and followed by an ISI of approximately 1000ms (+/- 200ms) during which time the screen was grey.

5.1.4 Results

Prediction 2A(i): Waveform morphology: WS no significant difference from controls (N170, and therefore P2, equivalent to controls)

There were no significant differences between amplitudes and latencies of P1 ($F(1,12)=.12$; $F(1,12)=1.78$, P=NS), N170 ($F(1,12)=1.93$; $F(1,12)=3.01$, P=NS) or P2 ($F(1,12) = 1.78$; $F(1,12) = .21$, P=NS) for the WS adult group compared to the typical controls (see Figure 5.1).

Discussion 2A(i)

These results confirm the prediction, showing no evidence of reduced amplitude N170 to car stimuli, in contrast to that to faces. They suggest that the structural encoding of faces is atypical and not the encoding of other objects (as represented by cars) compared to controls. On the other hand, these results may merely reveal that the control group morphology changed for cars compared to the morphology to faces. It is possible that the WS group waveform is unchanged for cars compared to faces. In other words, the question remains as to whether people with WS use the same system to process objects and faces, although it appears that cortical activation to objects is similar to that of controls.

It would be erroneous to assume on the basis of these results that object encoding in WS is 'intact'. This is unlikely to be the case for at least four reasons. First, behavioural results indicate that object encoding in WS is atypical. The passive viewing paradigm may not be sensitive to the WS abnormalities of object encoding, since even typical adults are likely to encode objects analytically rather than holistically, unless the stimuli are specifically designed to elicit such encoding (see Chapter Seven). Second, the experiment was limited in sensitivity, due to the small

number of participants. However, it was sensitive enough to test for an effect size similar to that for human faces. It is true to say that any possible differences were much less evident than those between WS and control adults viewing faces, and that these results compliment those reported by Mills et al. (Mills et al., 2000). In this sense, object encoding can be said to be less atypical than face encoding in this paradigm. Third, the trajectory of development was not examined. It is possible that the electro-cortical responses of adults with WS may have undergone atypical development before reaching normal-looking morphology. This is addressed in the next experiment, investigating car processing in adolescents. Finally, although cars have been used previously as examples of generic 'object' stimuli, it is possible that cars also are a special kind of stimulus with which most people, including those with WS, have considerable experience. It may be that other non-human-face visual stimuli would have elicited atypical results at the N170. This is addressed in Experiment 4A.

Prediction 2A(ii): Stimulus effects: No effect of inversion on latency for WS or control groups (cars processed differently to faces).

There was no main effect of condition ($F(1,12) = 2.18$, P=NS), or interaction of group with condition ($F(1,12)=.89$, P=NS).

Discussion 2A(ii)

These results suggest that the WS visual encoding is stimulus sensitive, because there was no effect of car inversion on latency. The analysis predicted and found a null effect. There are two potential problems with such predictions. First, significant effects may have been found if a larger sample size had been available. However, analysis suggests that the experiment did possess sufficiently high power (1-beta = .72) to detect differences the size of those found to human faces on the basis of the seven participants. Second, a non-significant difference in the electrical activity at the scalp does not necessarily mean that the cortical response is unchanged. It may mean that the changes are too small to be detected at the scalp, or that additional active mechanisms are not configured into the necessary open fields (see Methods

chapter). However, in this experiment the aim was to investigate whether the effect of object inversion was the same as or different from the effect of face inversion. The face inversion effect is extremely robust and would easily be detected on the basis of seven participants. This was not the case with the object inversion effect. In this respect it is possible to surmise that the effect of inversion was different for the two stimuli, although it is not possible to say what was the effect of car inversion, if there was any.

Prediction 2A(iii): No lateralisation, WS group no significant difference from controls

There was no main effect of hemisphere ($F(1, 12) = 1.32$, P=NS) or interaction of group with hemisphere ($F(1,12) = .74$, P=NS). However, topographical maps (see Figure 5.2) suggest that the WS group N170 was more negative over the LH, while the Control group showed no difference between hemispheres.

Discussion 2A(iii)

While the prediction was supported, in that there were no statistically significant effects, this may be because of the low sample size. Topographical maps illustrate that the WS group showed a tendency to left rather than right hemisphere lateralisation. This will be investigated in the next experiment, as it was for Experiments 1A and 1B, by analysing combined data from adult and adolescent groups.

5.1.5 Discussion

These results indicate that the encoding of object stimuli such as cars is less atypical than that of faces in WS adults. They also suggest that processing of faces is different from that of other objects, because of the difference in the effect of inversion. This experiment does not, however, reveal information about the difference or similarity between the systems underlying face processing versus object processing, nor does it shed light on the development of object encoding, since its focus was the adult endstate. This is discussed in the next experiment.

5.2 Experiment Two B– Developmental Trajectory during Adolescence

5.2.1 Introduction

The previous experiment showed that the electrocortical responses associated with object encoding in the adult endstate are less atypical than those associated with face encoding. However, object encoding may still have undergone an atypical developmental trajectory. As discussed in Preamble, the evidence from developmental neuroscience suggests that genetic mutation is unlikely to cause discrete effects on one cortical process (e.g., face encoding), but widespread effects that are more obvious for some processes than others (Karmiloff-Smith, 1998). In the current experiment adolescent data are explored in order to have directly comparable data to those of Experiment 1B. The expectation is that differences may be found between adolescents and adults with WS that will suggest that object processing in this syndrome is not fully developed at the end of childhood. Indeed, adolescents with WS will display abnormalities in their waveforms despite the apprently 'typical' waveforms seen in adults. In sum, the prediction is that even if the WS adult waveforms approximate 'normal' waveforms, the developmental trajectory by which they arrived at the phenotypic endstate will be atypical.

There were three predictions:

i) Waveform morphology: Atypical,
ii) Stimulus effect: No latency effect, no difference from controls,
iii) Topography: No lateralisation, no significant difference from controls.

5.2.2 Participants

Participants were 7 adolescents with WS (CA: 156 (26) months). Typically developing controls were individually matched to the WS participants (CA: 158 (25) months).

5.2.3 Results

Prediction 2B(i): Waveform morphology: Atypical

The waveform was severely atypical (see Figure.5.1). The P1 amplitude was larger for controls compared to WS adolescents ($F(1,12)=7.04$, $P<.05$), although there was no difference in latency ($F(1,12)=.27$, P=NS). The N170 deflection was present for the WS group only as a tiny deflection, which was positive in value. As a consequence there was a significant difference from controls ($F(1,12) = 4.62$, $P=.05$), for whom the N170 was a larger deflection. The N170 peak was also much later in controls ($F(1,12)=9.50$, $P<.05$), which was unsurprising given the comparative sizes of the deflections. As a consequence, N170 latency also affected the P2 latency, which peaked later for controls ($F(1,12)=6.97$, $P<.05$), although P2 amplitudes were not significantly different ($F(1,12) = 1.39$, P=NS).

Discussion 2B(i)

The prediction was supported in that the WS adolescent waveform for cars was atypical, unlike that of the WS adult. It suggests that although the adult endstate looks normal, it actually develops differently. Further studies are needed to highlight the exact differences in the adult system that may be present as a result of this unusual trajectory of development.

Prediction 2B(ii): Stimulus effect: No latency effect, no difference from controls

The prediction was supported in that, as for adults, there was no latency inversion effect on the N170 ($F(1,12)=.05$, P=NS), or interaction with group ($F(1,12)=.07$, P=NS).

Discussion 2B(ii)

There is no evidence using this task of abnormal encoding of objects. However, there is no evidence *for* normal encoding, because what is found is a null effect. Evidence for abnormal processing in WS would have been an increase in latency with the inversion of the car stimulus. However, it is possible that the differences in categories were too gross to elicit actively atypical processing in the WS group. This

is addressed in Experiment Four, using 'face' stimuli that are non-human and may be processed more like objects than like human faces in the typical group.

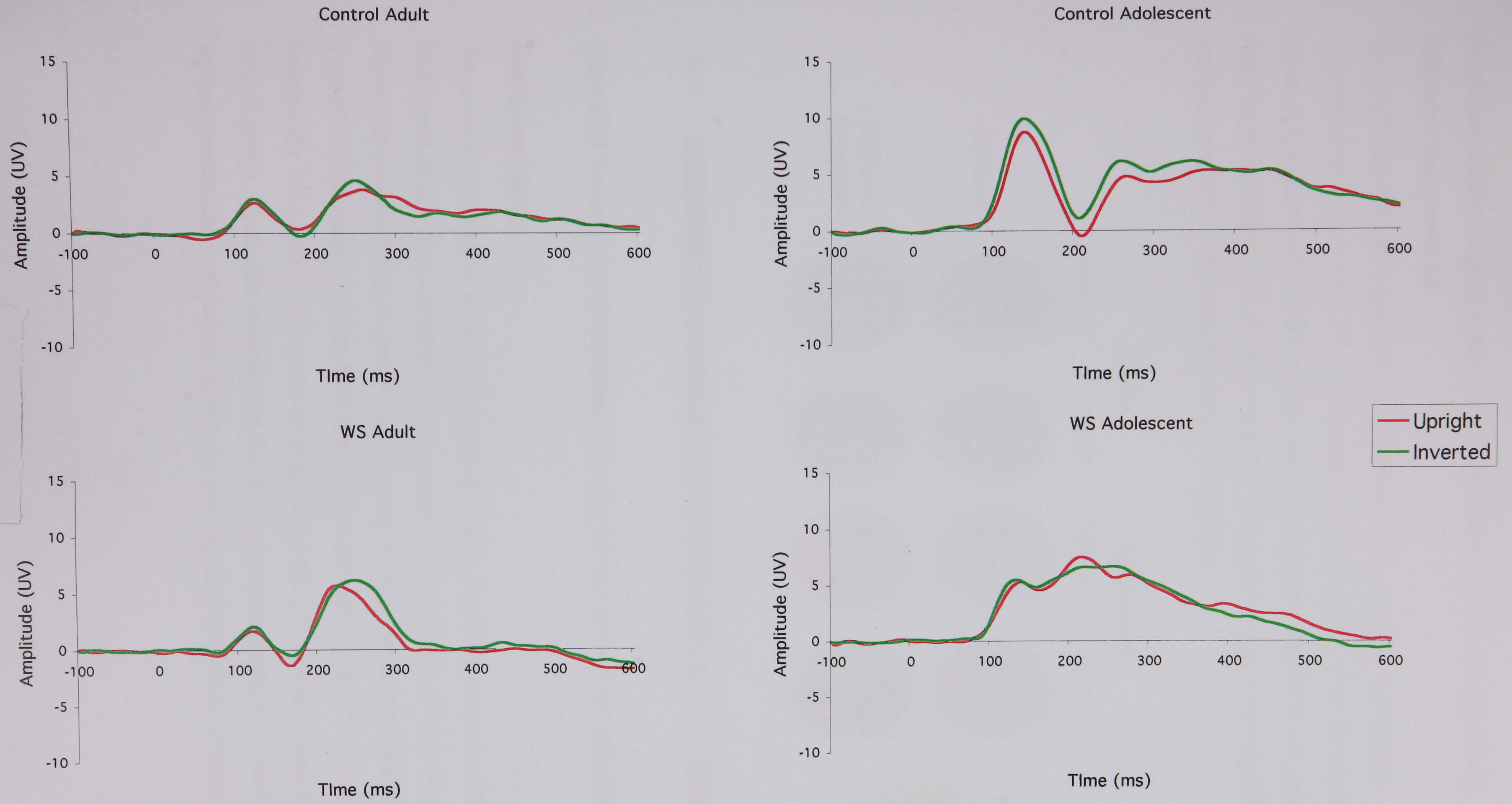


Figure 5.1 Average Waveforms for Upright Compared to Inverted Car Stimuli

Prediction 2B(iii): Topography, no lateralisation of N170, no significant difference from controls

The prediction was not supported because there was a group by hemisphere interaction, ($F(1,12) = 4.91$, $P<.05$). Topographic maps of the N170 are illustrated in Figure 5.2. These show that the control adolescent group component was clearly right lateralised ($t(6)=2.23$, $P<.05$), while the WS group showed a non-significant tendency toward left lateralisation ($t(6) = .65$, $P>.05$).

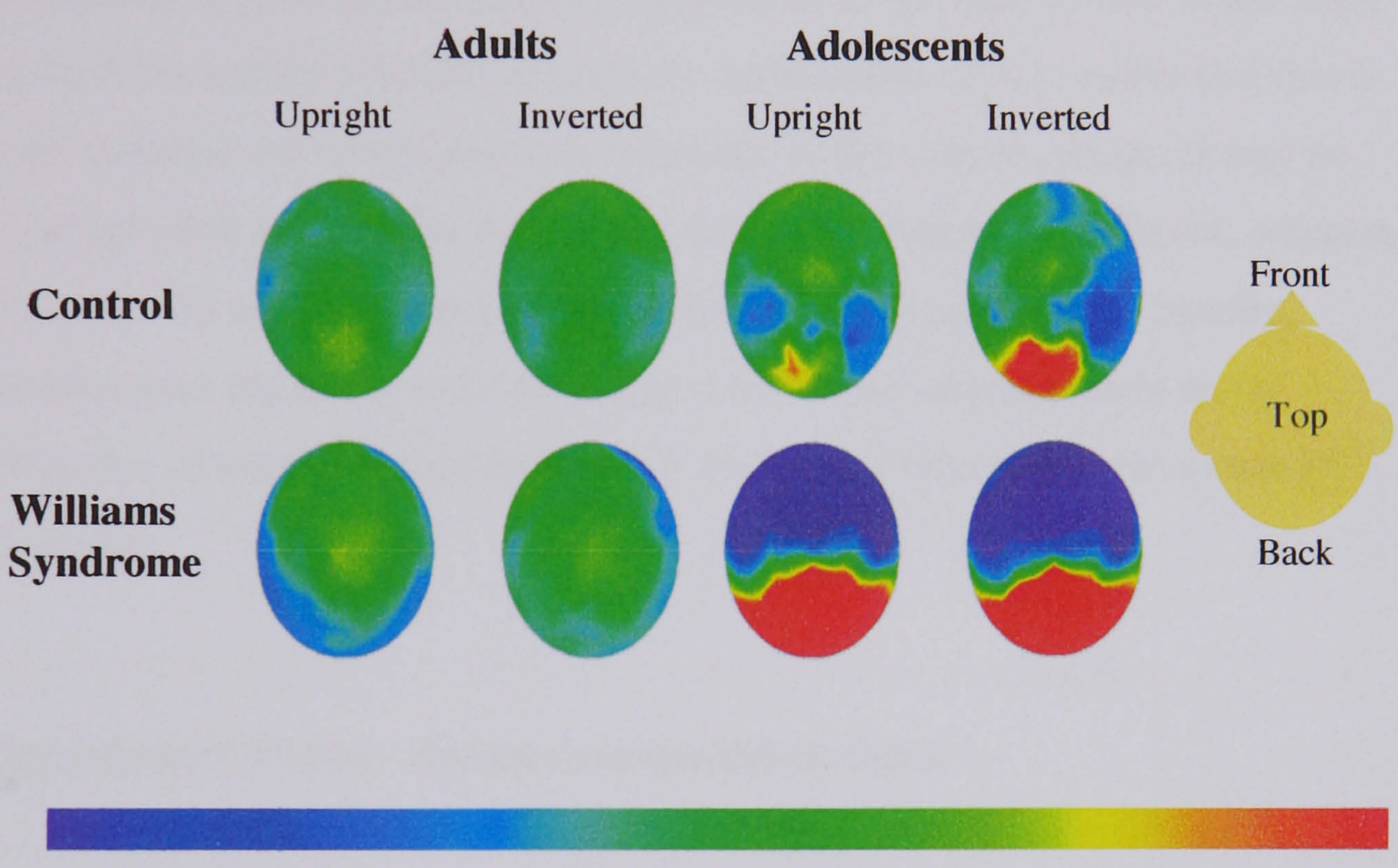


Figure 5.2 Topographic Scalp Maps Showing N170 Peak to Car Stimuli

Discussion 2B(iii)

These results are similar to those of the adult groups. For this reason, the adult and adolescent groups were combined and analysed for hemispheric differences in N170. There was no main effect of group ($F(1,26) =.90$, $P=NS$), but as predicted there was a crossover interaction of group with hemisphere ($F(1,26) = 4.86$, $P<.05$). This was because the WS group N170 was more negative on the LH, and vice versa for the control group. These data indicate that the object processing system, as well as that for face processing, is abnormal in WS. As also argued on the basis of behavioural

data (Karmiloff-Smith, 1998), it is not the case that one system is 'intact' and the other 'impaired'.

5.2.4 Upright and Inverted Cars Summary

The results of this experiment suggest that the processing of cars is different from the processing of faces in WS, as it is for the typical controls. However, it also suggests that object encoding, like face encoding, undergoes atypical development throughout adolescence. The difference is that the electrocortical atypicalities in the object processing system are less obvious than those of the face system in the adult endstate, but both appear similarly atypical in adolescence. It is possible that this is because all statistics are computed with reference to the control groups. It may be that the typical adult systems for processing faces and objects are different, whereas the adults with WS use the same system for both kinds of processing. Equally, typical adolescents are likely to be revealing a developed object system and a developing face system, whereas for the WS adolescent both may be in a state of atypical change.

5.3 Experiment Three - Faces Compared to Cars

5.3.1 Introduction

Experiments 2A and 2B indicated that the processing of objects was different from the *processing* (stimulus effects) of faces in both the adult and adolescent WS groups, but the results were unable to allow a comparison of the electophysiology of the *system* (waveform morphology, topography etc.) used for processing faces or cars. In response, the current experiment was designed to directly compare faces with cars for WS adults and adolescents, and controls. There were four predictions for each group:

Adults

i) Morphology Replication: WS human face N170 smaller amplitude than controls

ii) Morphology Replication: WS car N170 no significant difference from controls

iii) Stimulus effects: N170 larger and later to faces for controls, but not WS group

iv) Topography: Different topography N170 for faces compared to cars for controls, but not WS group.

Adolescents

i) Morphology Replication: WS Human face N170 smaller amplitude than controls

ii) Morphology Replication: WS Car N170 significantly smaller than controls

iii) Stimulus effects: N170 larger and later to faces for controls, but not WS

iv) Topography: Different topography N170 for faces compared to cars for controls but not WS group.

5.3.2 Participants

Adult groups: 9 adults with WS. Of these individuals, only 6 (CA: 370 (142) months) yielded usable data (loss due to excessive eyeblink and movement artefacts) and were individually matched to typical controls (CA: 372 (141) months).

Adolescent groups: 8 adolescents with WS. Of these individuals 6 (CA: 152 (25) months) yielded usable data and were individually matched to typically developing controls (CA: 153 (24) months). Data were lost for the same reasons as for the adult group.

5.3.3 Stimuli

Stimuli were 25 cars and 25 faces chosen at random from those used in Experiments One and Two. Stimuli were greyscale and matched for visual angle. Face and car stimuli were mixed into one block and in a different random order for each participant. Presentation was for 500ms, preceded by a baseline period (small white square in the centre of the screen) of approximately 300ms, and followed by an ISI of 1000ms (+/- 200ms).

5.3.4 Results

Interpretation of all data was limited, due to the small number of participants for each group. The large participant loss may have been due to the nature of the stimuli. All faces and cars were fairly small and in greyscale, making them boring and tiring to attend to. This was commented on by over half of the individuals taking part. Future experiments should use colour stimuli, or some method of retaining attention such as a button press. Due to the low numbers, all predictions are reported by visual inspection, comparing each individual waveform with the relevant control waveform. This description is then followed by statistical tests.These analyses are based on a tiny sample size and should, therefore, be interpreted with caution.

Adults

Prediction 3A(i): Morphology replication: WS Human face N170 smaller amplitude than controls

Replication was confirmed by visual inspection, and a significant statistical difference was found ($t(10) = 2$, $P < .05$ one way).

Prediction 3A(ii): Morphology replication: WS Car N170 no significant difference from controls

Visual inspection suggested a small difference, in that the WS N170 appeared somewhat smaller (see Figure.5.3). However, this was not statistically significant ($t(10) = 1.51$, P=NS).

Prediction 3A(iii): Stimulus effects: N170 larger and later to faces than cars for controls, but not WS (no difference in WS group)

Visual inspection did not support the prediction for amplitude: Four WS participants showed a tiny difference (upto 1 μv) because the face N170 was larger than that to cars; one participant showed no difference; and one showed an N170 that was slightly larger to cars than faces. In contrast, for the control group there was always a clear difference (mean 5μv) for all individuals, because the face N170 was always

larger than the car N170. The implication is that the tiny but typical effect in the WS group was due to chance. This observation was supported by a 2x2 ANOVA which resulted in a trend towards a main effect of group ($F(1,10)=3.85$, $P=.078$ because, as expected, the car and face combined average N170 was smaller for the WS group), and a significant effect of condition ($F(1,10)=8.38$, $P<.05$) but no interaction of group with condition ($F(1,10) = .39$, P=NS). It should be noted, however, that the dataset is really too small to justify the use of statistical tests investigating interactions, and a lack of a significant difference is hardly surprising! Figure 5.3 illustrates the average waveform for faces compared to cars for control and WS adults. It shows that the morphology to cars looks very different from that for faces for the control adults, but not for the WS group. The WS adult waveform is very similar for both stimuli.

Visual inspection of N170 latency supported the prediction because the component peaked later to faces than to cars for the control group only. There was no difference at all in the WS group latency for faces compared to cars. In other words, there was no main effect of condition ($F(1,10) = .24$, P=NS), but there was a group by condition interaction ($F(1,10) = 6.38$, $P<.05$). This was because the faces peaked significantly later than cars for the control group alone (WS: $t(5) = 1.01$ P=NS, Control: $t(5) = 1.93$, $P = .05$). Again, it should be noted that such statistical tests are not strictly legitimate for use with such small sample sizes and were used cautiously only to confirm visual inspection.

Discussion 3A(iii)

These data offer evidence that the WS N170 lacks specificity to faces. The amplitude and the latency of N170 are relatively insensitive to stimulus. This suggests that the between group differences noted in waveform morphology to faces alone are because the WS participants process faces more like cars. In contrast, the control group waveform is highly stimulus specific.

Prediction 3A(iv): Topography: Different topography N170 for faces compared to cars for Controls, but not WS group.

Visual inspection indicated that N170 was more right than left lateralised for the control group for both faces and cars, whereas the component was bilateral for the WS group. There was no indication of different topographies to the different stimuli for either group. Statistical analysis indicates that there was no main effect of hemisphere ($F(1,10)=.02$, P=NS), but there was a group by hemisphere interaction ($F(1,10)=4.81$, $P<.05$) which was not affected by condition (no three way interaction ($F(1,10) = .04$, P=NS)). The interaction of group by hemisphere was significant, however, because the WS N170 was more negative over the LH than RH ($t(5)=1.97$, $P=.05$) while the Control group did not significantly differ. This surprising result is confirmed using normalised data (see methods, $F(1,10) = 4.79$, $P <.05$), and can be explained by attention to the standard deviations of the means. Mean amplitudes differed across hemisphere only by approximately 0.6uv in the WS group, but standard deviations were low and very similar for both hemispheres (Mean amplitude LH =-2.67 (.98) versus RH –2.06(1.13)). This is different from the control group, for whom variance was greater (Mean amplitude LH = -3.85 (1.72), RH = -4.38 (2.26)) across hemispheres and therefore power to detect the difference between them was lower.

Discussion 3A(iv)

The prediction was not supported because there was no difference between the topography for faces compared to cars in either group. However, the evidence does confirm the finding in Experiment 1A of overall abnormal lateralisation of function in the WS group.

Adolescents

Prediction 3B(i): Morphology Replication: WS Human face N170 smaller amplitude than controls

The prediction was confirmed by visual inspection (e.g., mean WS = 1.56; Control = -1.26) but not by statistical analysis (t(10)1.71, P=NS), which suggested that there was no difference between groups.

Prediction 3B(ii): Morphology Replication: WS Car N170 significantly smaller than controls

The prediction was confirmed by visual inspection and by statistical analysis (t(10)= 1.81, P=.05).

Prediction 3B(iii): Stimulus effects: N170 larger and later to faces than cars for controls, but not WS (no difference in WS group)

The amplitude prediction was inaccurate for both controls and WS adolescents. Visual inspection was confirmed by statistical analysis showing that for both groups the N170 amplitude was larger to cars than to human faces (F(1,10)=12.2, P<.05). There was no interaction of stimulus with group (F(1,10)=.51, P=NS).

Visual inspection indicated that the WS adolescent group (like the WS adult group) did not vary in latency in response to the two stimuli, in contrast to the Control adolescent group whose N170 peaked later to faces. This was confirmed by descriptive data. Mean peaks were at exactly the same time for faces and cars for the WS group (see Figure 5.3), but were 8 ms later to faces for the control group. Unfortunately, this difference was not robust enough to give rise to a group by condition interaction (F(1,10) = 1.69, P=NS), presumably because of the tiny sample size. Again, the small N severely limits interpretation of statistical tests.

Discussion 3B (iii)

These results suggest that despite the abnormal appearance of the N170 in WS adolescents, its amplitude does vary with stimulus in the same way as controls.

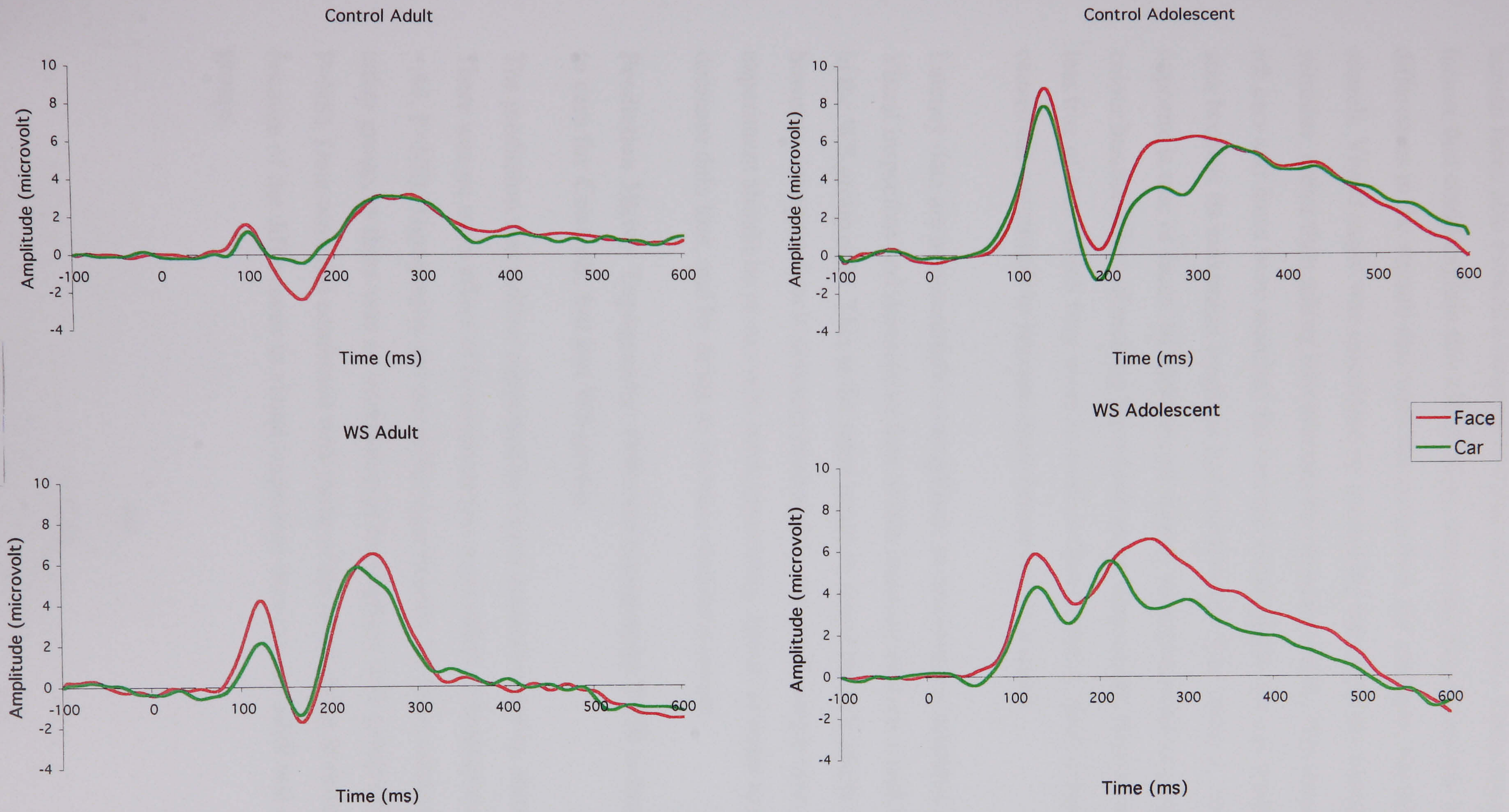


Figure 5.3 Average Waveforms to Faces Compared to Cars

(Within Experiment)

However, it is unclear why the result was found in the typical adolescent group that cars evoked a larger N170 than did human faces. This does not support the data on children and adolescents presented by Taylor et al. (Taylor et al., 1999) in which human faces also evoked a larger N170 than other objects. There are a number of factors that could explain this effect. First, there may have been low-level feature differences in the stimuli that were not controlled, for example, the size of the stimuli. Visual angle was calculated by measuring the top to the bottom of the stimulus, rather than taking into account the stimulus width. This means that though the cars and faces were matched for vertical visual angle, the car stimulus is larger in area because its maximum length is horizontal rather than vertical, whereas the opposite is true of faces. In addition, all stimuli were presented in greyscale. Lack of colour has the effect of making faces look more than usually homogenous, but this is less true of cars which vary more in contour than do faces. Such a factor may have caused the car stimuli to become more interesting as a result.

Latency data are as meaningful as amplitude in determining stimulus specificity. Visual inspection and descriptive data of this measure indicate a lack of specificity in the WS group only. This is the same result as found for WS adults. Unfortunately, however, interpretation is severely hindered by the small sample size. Ideally the experiment should be re-run with more interesting stimuli in order to attempt to decrease data loss, and by doing so increase statistical power.

Prediction 3B(iv): Topography: Different topography N170 to faces compared to cars for Controls, but not WS group.

The prediction was neither supported by visual inspection nor by statistical analysis. There was no main effect of hemisphere (no main effect of hemisphere ($F(1,10) = .44$, P=NS). Topography did not differ significantly for faces compared to cars in either group, as there was no interaction of hemisphere with group ($F(1,10) = 1.10$, P=NS). Data were not combined with those of the adult group in order to increase N, because of the differences in visual inspection between the adult and adolescent groups.

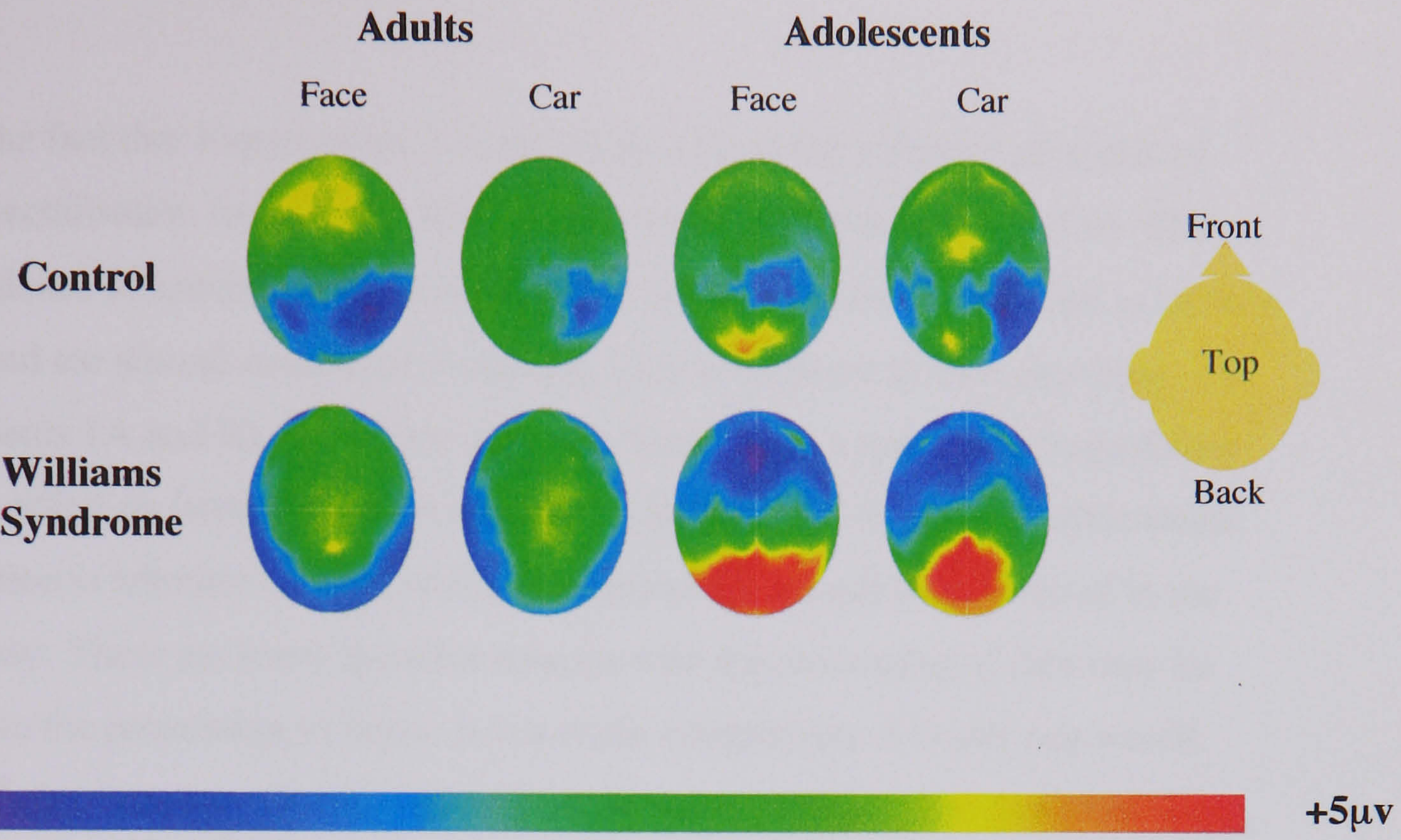


Figure 5.4 Topographic Scalp Maps Showing N170 to Faces Compared to Cars (Within Experiment)

5.3.5 Faces Compared to Cars Summary

The interpretation of this experiment was severely limited by the low sample size. However, support was given for the previous experiments in showing the same abnormalities of the N170 component to faces but not to cars in adults, overall atypical hemispheric lateralisation, and atypical development throughout adolescence. The results indicate that there is a lack of specificity in the amplitude and latency of the adult WS N170 to faces compared to cars. The apparent stimulus sensitivity of the WS adolescent data may be artefactual. Overall, the results indicate that there is less specialisation of the WS system for faces compared to other objects (at least as represented by cars), compared to typical controls.

5.4 Chapter Five Summary

Despite the fact that Experiments 3A and 3B provide some evidence of a lack of *system* specialisation for faces in WS, the previous experiments (2A and B) offer some evidence of specialisation of *processing,* since there was no increase in latency for inverted car stimuli compared to upright. This is different to face encoding (Experiments 1A and B), for which there was found to be a normal and significant inversion effect on latency (but not amplitude) for both WS adults and adolescents. The question is whether the processing of human face stimuli is specialised in the *normal* way. There are many possible reasons why the processing of cars may be different to the processing of faces. It is a crude comparison. A better one would have been that between stimuli which share the same configuration as human faces, but belong to a different category of stimulus. A good example of such stimuli are monkey faces. Specialisation for human faces over monkey faces has been demonstrated in the typical adult (de Haan et al., In press). Such sensitivity of the N170 response is thought to develop directly as a result of experience with individuation of con-specifics. The role of experience, in determining the specificity of the WS N170 component, is investigated in the next chapter.

Chapter Six

The Role of Experience

6 The Role of Experience

6.1 Experiments Four A and B

6.1.1 Introduction

Experience is a critical factor determining the changes of face encoding over typical development. It is experience with the faces of con-specifics that is thought to underlie the increasing dependence on configural processing that is reflected in the human face inversion effect. One of the ways that this has been demonstrated is by comparing the effect of inverting a human face with that of inverting a monkey face. Monkey faces share the gross configuration of human faces, yet most people have little experience with discriminating between such stimuli. As a consequence, when monkey faces are inverted, there is no significant decrease in recognition accuracy, or increase in reaction time (Wright & Roberts, 1996).

The lack of inversion effect to monkey faces is reflected in the N170 component in typical adults. Upright monkey face stimuli have been shown to elicit an N170 that is as large as that to inverted human faces (i.e. larger than that to upright human faces) although it peaks later. However, monkey face waveforms do not increase in latency or amplitude with inversion (de Haan et al., In press). The large N170 is thought to occur because of the presence of similar features to human faces (eyes, nose, mouth in roughly triangular arrangement), which causes the encoding system to increase in activation in order to detect as human face/non-face. The delay in latency, compared to human faces, is consistent with the evidence from previous studies showing the same effect to be due to the increase in detection difficulty. The lack of inversion effect to monkey faces supports the hypothesis that encoding takes place on the basis of features, rather than the configural relationship between features, which do not vary when the stimulus is turned upside down.

The infant face-sensitive component, equivalent to the adult N170, does not appear to be specialised for human faces in the same way as adults (de Haan et al., 1998). At six months of age the face-sensitive component, the P400, is a positive deflection in the ERP which peaks at approximately 350ms after stimulus onset. It is face-sensitive in being shorter in latency to faces than to objects. Also, the component decreases in amplitude with human face inversion. However, it turns out also to be sensitive in the same way to the inversion of monkey faces. This suggests that the face processing system in infancy is more 'broadly tuned' than that of adults. The hypothesis is that the system gradually becomes more specific to the faces of con-specifics with increasing experience.

Experiments One to Three have demonstrated that the N170 in individuals with Williams Syndrome does not differ in sensitivity to faces and objects. It does not show the normal increase in amplitude with face inversion, and appears to undergo an abnormal developmental trajectory. It also appears to be more left than right lateralised, which is in contrast to most (about 80%) typically developing individuals. Overall the evidence is consistent with people with WS displaying an abnormally developed system for configural encoding. It may be, then, that the N170 component is a more broadly tuned electro-cortical response in WS, which is less specialised for human faces and depends more on featural than configural information for all stimuli. The presentation of monkey faces is another way of testing this hypothesis and the role of experience. They are different to other non-face stimuli in eliciting a larger N170 than human faces in typical adults (unlike cars and objects that elicit a smaller component). This appears to be because of the highly specialised nature of the adult human-face processing system. In other words, this is an extremely conservative test for the sensitivity of the WS response. Only if the WS system is highly specialised should there be a difference between the monkey and human face processing and the system used to carry out that encoding. This hypothesis generates three predictions for the WS adult endstate:

i) Morphology: WS small N170 and large P2 compared to controls (as for human faces),

ii) Stimulus effects: Significant increase in latency with monkey face inversion (as for human faces) for WS group but not controls,

iii) Stimulus effects: WS no difference in waveform to upright monkey compared to upright human faces or cars,

iv) Topography: WS left lateralised N170.

6.1.2 Participants

The adult group comprised 9 individuals with WS; of these 8 (CA: 359 (145) months) yielded usable data and were individually matched to typical controls (CA: 365 (147) months). The adolescent group comprised 8 individuals with WS (CA: 157 (24) months) individually matched to typically developing controls (CA(158 (23) months).

6.1.3 Stimuli

Stimuli were the same as those used in (de Haan et al., In press) and consisted of 25 colour pictures of adult monkey faces randomly presented at 12.1 degrees visual angle a total of 200 times, with 50% of the stimuli in the inverted position. Presentation was for 500ms, preceded by a baseline period of approximately 300ms (small white fixation square) followed by an ISI of approximately 1000ms (+/- 200ms) during which time the screen remained blank grey.

6.1.4 Results

Adults

Prediction 4A(i): Morphology: WS small N170 and large P2 compared to controls (as for human faces)

The prediction was supported. Waveform morphology differences between adult groups were identical to those found for human face stimuli. The P1 was of comparable size, although peaked later ($F(1,14)=5.51$, $P<.05$), the N170 was

smaller, (-2.51μv ; -7.35μv) leading to a main effect of group ($F(1,14)=8.12$, $P<0.05$), and the P2 was larger (7.83μv:3.81μv, $F(1,14)=4.38$, $P=.05$). There were no differences in the latencies of N170 ($F(1,14) = 2.61$, P=NS), or P2 ($F(1,14)=.22$, P=NS).

Discussion 4A(i)

The WS waveform to monkey faces was very similar to that displayed to human faces, and was different from controls. This appears to be because the waveform to faces or objects does not differ in WS as much as it does in controls. The waveform to all faces in WS is much more similar to the control 'object waveform' than to the control 'face waveform'. These data support the hypothesis of a lack of specialisation of the face processing system in WS.

Prediction 4A(ii): Stimulus effects: Significant increase in latency with monkey face inversion (as for human faces) for WS group but not controls

The analysis of WS and typically developing adults groups revealed a surprising tendency for the inverted face to peak later than the upright ($F(1,14)=4.54$, $P=.051$).

Discussion 4A(ii)

The prediction was supported for the WS group but not for the control group. At a superficial level this appears to make the WS data difficult to interpret, because it is both similar to the control group and to the human face inversion effect. However, though the monkey inversion effect is in the same direction as that of the human face inversion effect for both groups, the difference in conditions is much smaller in size. The latency difference between upright and inverted monkey faces was, on average, approximately 2ms and was not significant in individual adult group analyses (WS $F(1,7)=2.24$, P=NS; Control, $F(1,7)=2.34$, P=NS). By contrast, the latency difference for human faces was approximately 9ms and was significant in individual analyses (see Experiment 1A). In other words, the WS monkey face inversion effect was no different from controls. In both groups the effect was different from the human face inversion effect. This suggests that the WS face processing system is specialised for

human faces compared to monkey faces and that therefore it is, to some extent at least, modularised like typical adults and not like typical infants.

These data support and extend the findings presented in Chapters Four and Five. They show that *processing* in WS is different for stimuli that share the same configuration as human faces. Both are also different from the processing of objects.

Prediction 4A(iii): Stimulus effects: WS no difference in waveform to upright monkey compared to upright human faces or cars

Unfortunately it was not possible to undertake legitimate statistical analysis of the differences between monkey faces and the other stimuli. This was because one WS individual's data were discarded in this experiment, and two sets of data were discarded in the car experiment, leaving only 5 participants whose data were used for all three experiments. The power of the analysis would therefore be too low to pick up any group by condition interactions. In addition, the experiments were not all run in the same session or on the same day, which means that a number of factors (such as fatigue) could have affected the size or timing of the ERP components. Finally, it was not possible to closely match the stimuli for low-level stimulus features (like spatial frequency) since these naturally vary between the classes used.

Despite these caveats, Figure 6.2 shows the average waveforms (for the upright condition) from Experiments One, Two and Four. This revealing across-study comparison supports the within-study comparison presented in experiment three in which, for adults with WS, there was a lack of difference in amplitude between face and car stimuli. From Figure 6.2 there appears to be no difference between human and monkey faces or cars (amplitude or latency of N170) for the WS group, despite there being a huge difference between human and monkey faces compared to cars for the control adults. This finding is striking in scale and offers support to the statistical analysis in the previous experiments, which suggest a lack of system specificity in the WS group.

Late effects, up to 600ms, are also displayed on the waveform maps. These were not statistically analysed in any of the current experiments, although future work should attempt to do so. However, visual inspection supports the lack of specificity of the WS waveform. There appears to be no difference in later WS waveform for any of the stimuli, in contrast to the control adult waveform, in which human and monkey faces clearly separate from that for cars.

Prediction 4A(iv): Topography: WS left Lateralised N170

There was a suggestion of more left than right activity in WS (see Fig 6.3) but the effect, as for human faces and cars, was very small. Consequently there was no significant main effect of hemisphere ($F(1,14)=.00$, P=NS) or interaction of group with hemisphere ($F(1,14)=.65$, P=NS).

Discussion 4A(iv)

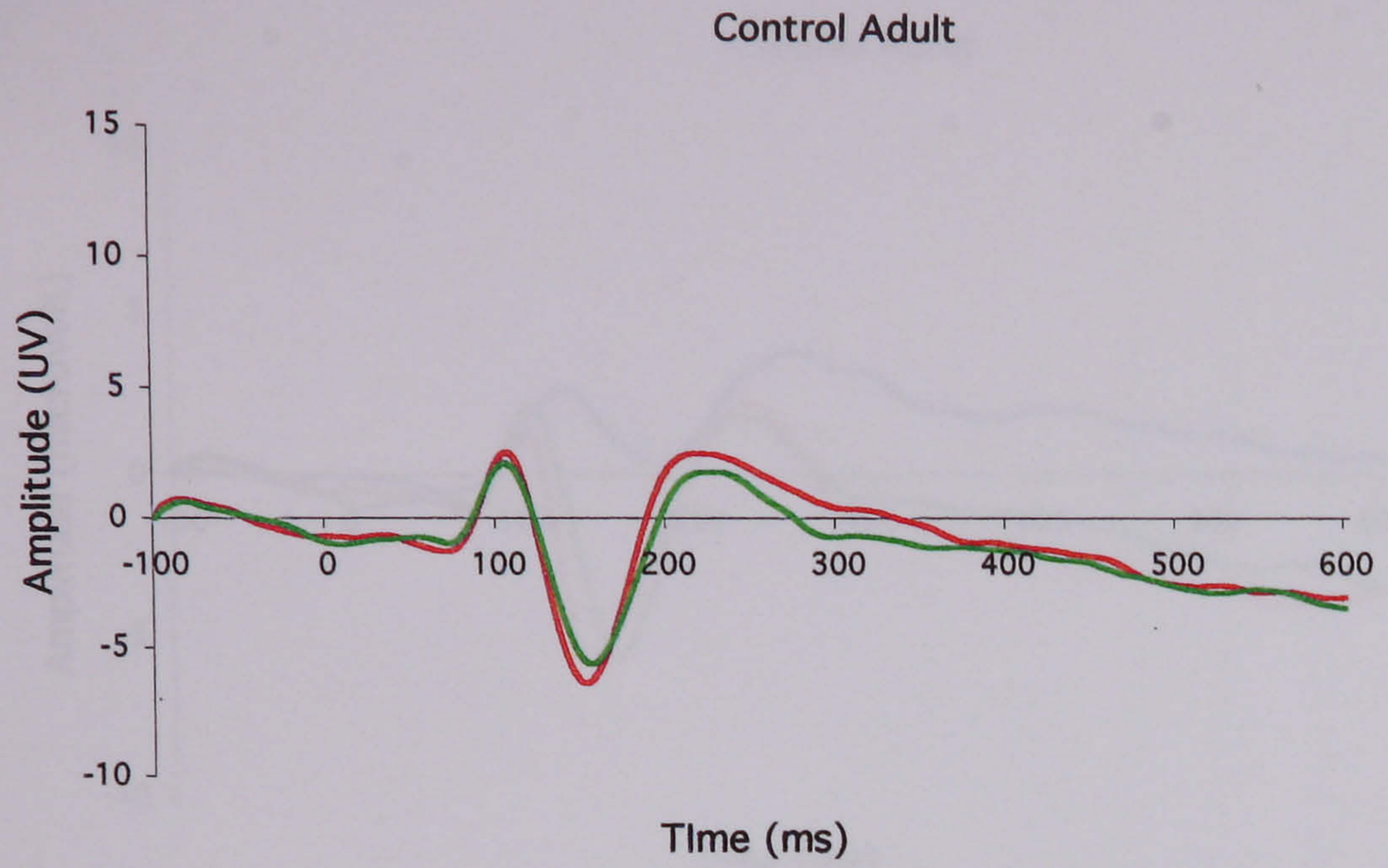
These results are similar to those for human faces. Topographic information does not dissociate monkey from human face processing in either control or WS groups.

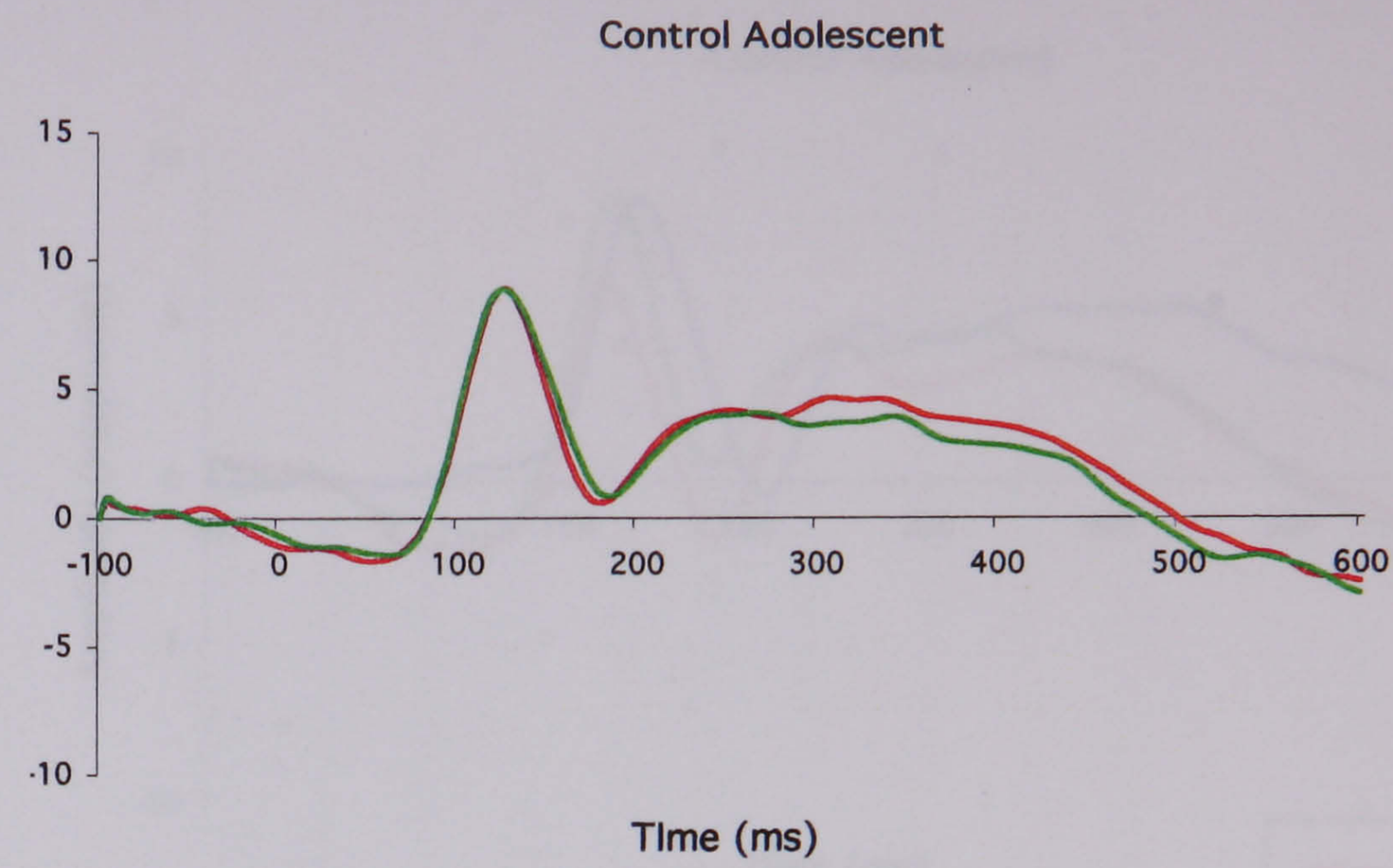
Adolescents

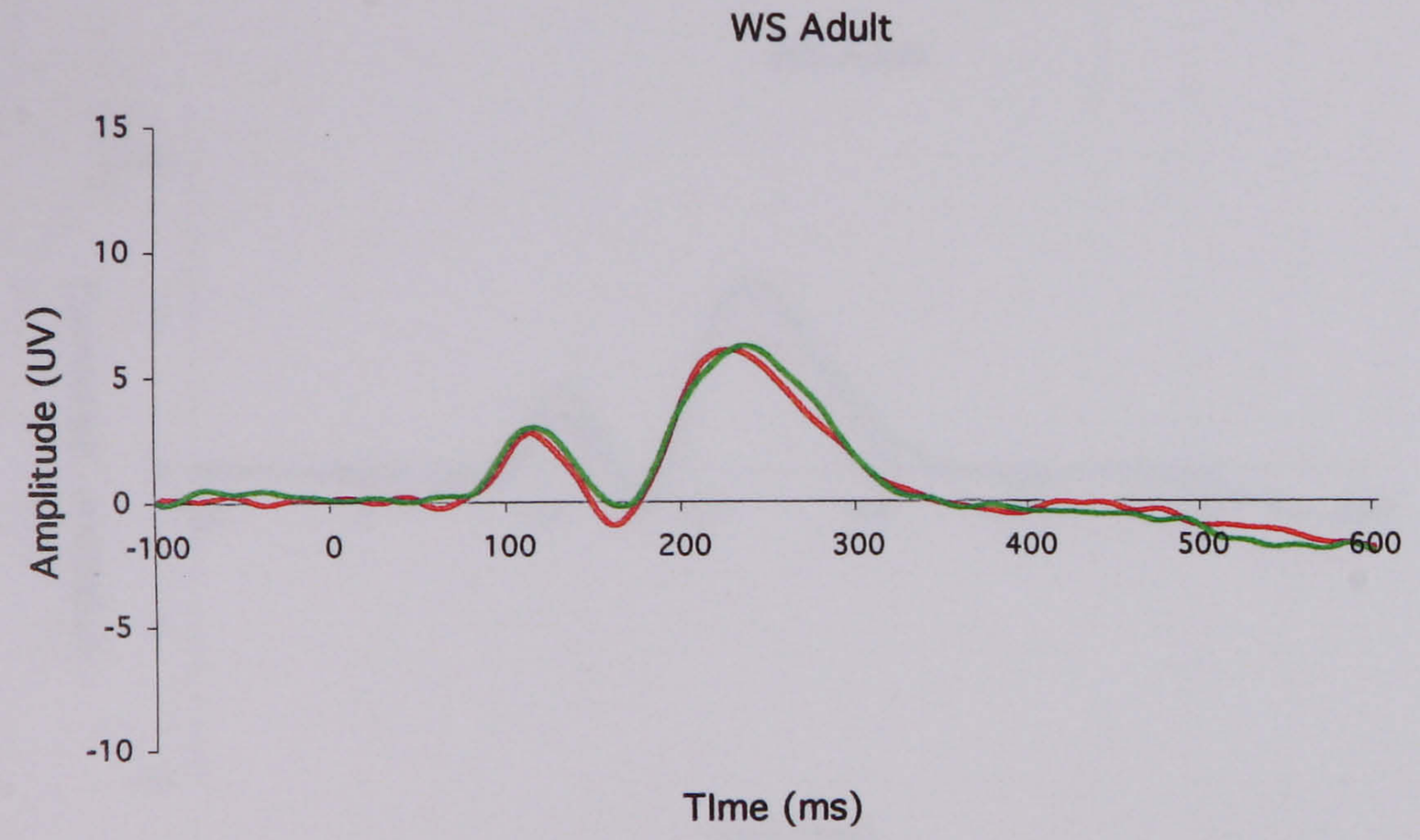
Prediction 4B(i): Morphology: WS small N170 and large P2 compared to controls

The differences in waveform morphology in WS and typical adolescent groups were similar to those between the two adult groups. The P1 was similar in size and latency, the N170 deflection was much smaller (positive in value) in the WS group (3.91μv; -1.42μv, ($F(1,14)=7.93$, $P<.05$)), and the P2 appeared amplified (11.47μv; 6.40μv, ($F(1,14)=14.06$, $P<0.005$)). However, there were also surprising differences; the control group deflections took longer to peak for both the N170 ($F(1,14)=6.41$, $P<.05$) and the P2 ($F(1,14)=6.89$, $P<0.05$) components.

The N170 was differently lateralised between groups ($F(1,14)=4.86$, $P<.05$) because the WS group amplitudes were more negative on the left than the right ($F(1,7)=8.29$, $P<.05$) whereas the controls did not differ.







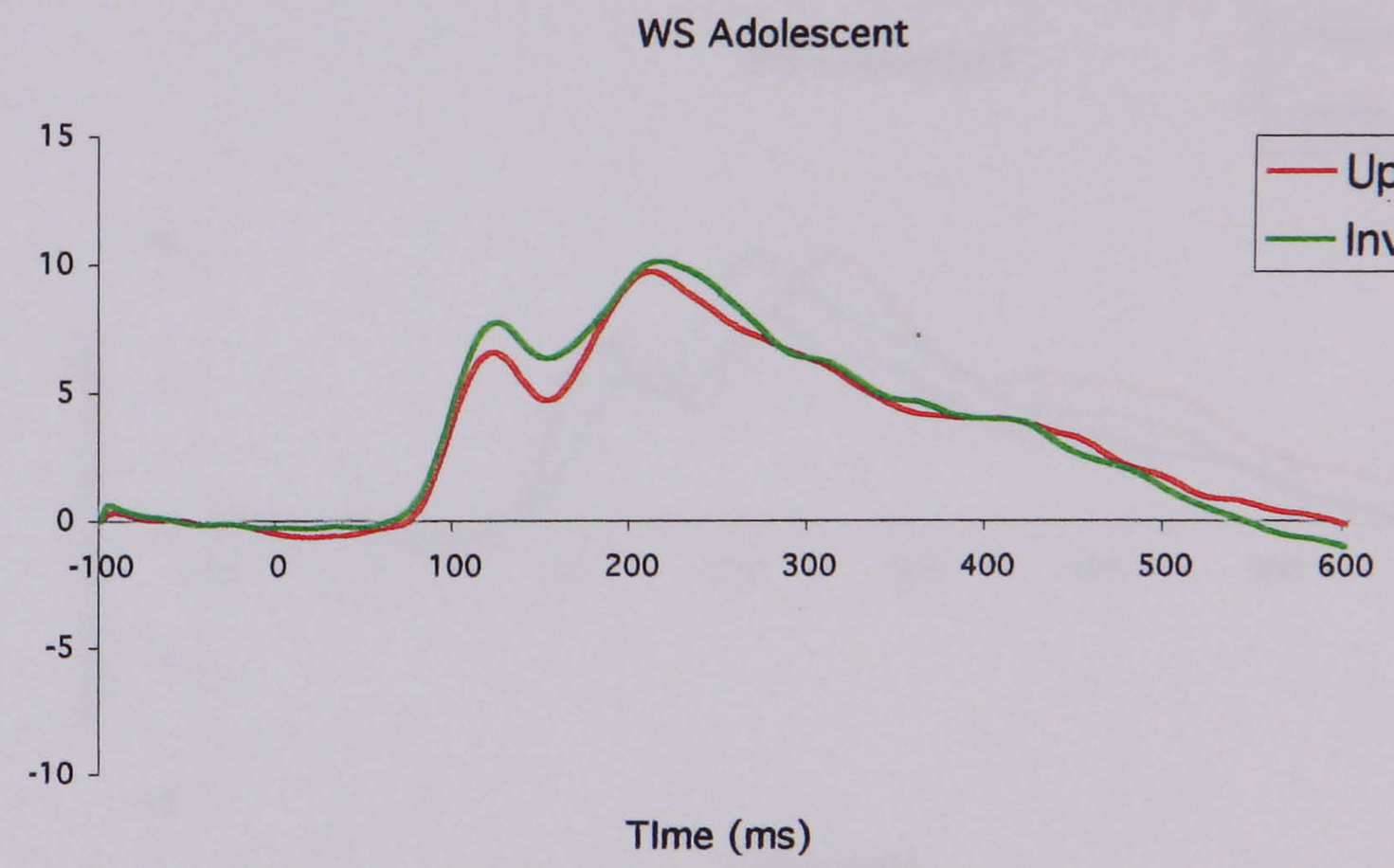


Figure 6.1 Average Waveforms to Monkey Faces

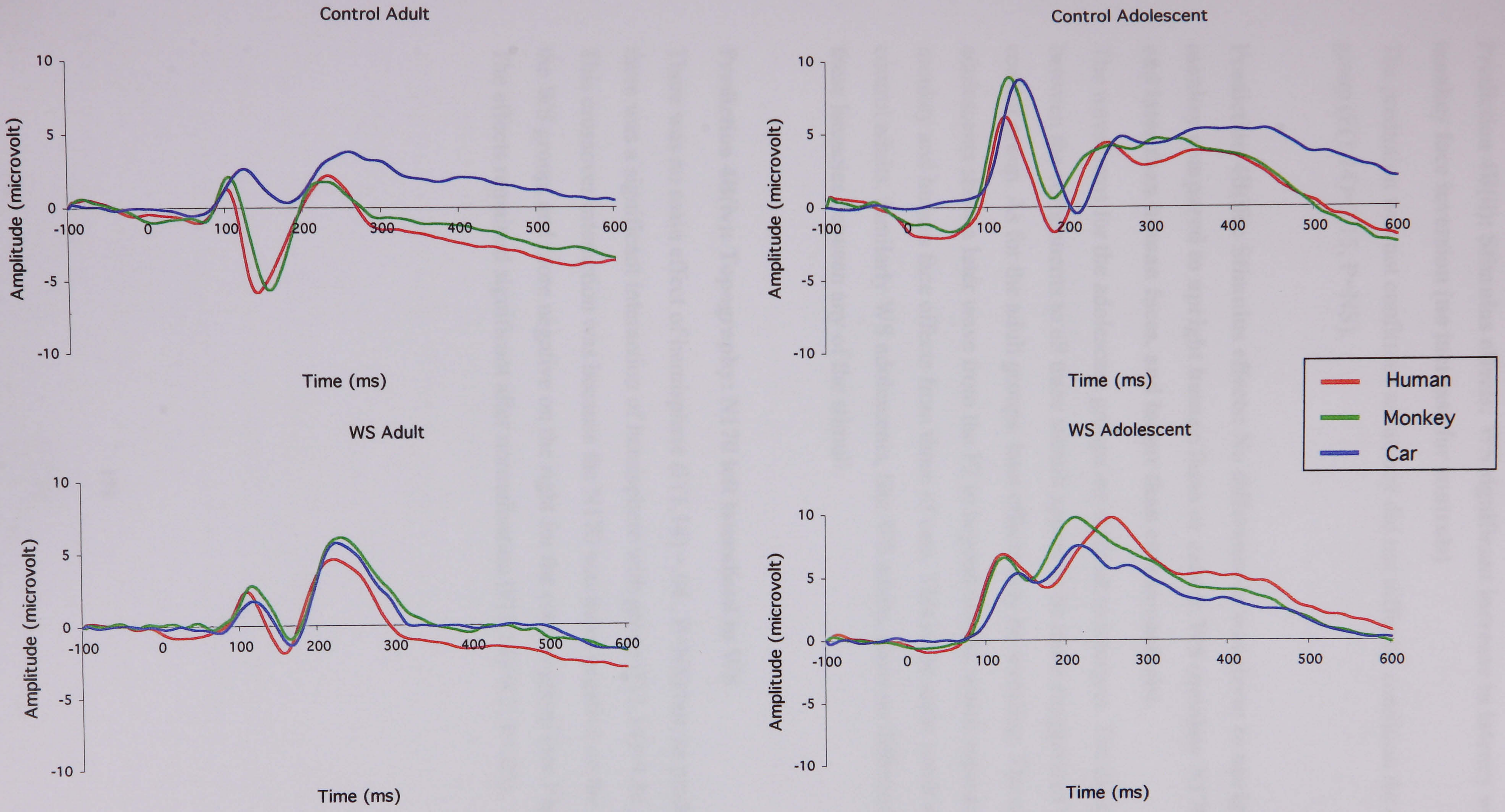


Figure 6.2 Average Waveforms to Upright Human, Monkey and Car Stimuli

Prediction 4B(ii): Stimulus effects: WS significant increase in latency with monkey face inversion (no increase for controls)

The prediction was not confirmed as latency did not differ by condition for either group (F(1,14)=2.15, P=NS).

Prediction 4B(iii): Stimulus effects: No difference in waveform to upright monkey compared to upright human faces or cars in WS (monkey N170 larger and later than human faces, and larger than cars in controls).

The waveforms for the adolescent groups are difficult to interpret. The differences between the components to all three stimuli appear to be more exaggerated for the control group. As for the adult groups, later effects may be revealing. The control adolescents show a later wave from the P2 to beyond 600ms, which separates monkey and human face effects from those of cars. This is the same result as for control adults. Similarly WS adolescents, like WS adults, show no differentiation at these latencies between any of the stimuli.

Prediction 4B(iv): Topography: N170 left lateralised in WS

There was no main effect of hemisphere (F(1,14) =.04 , P=NS) but, as predicted, there was a significant interaction of hemisphere with group (F(1,14)=4.86, P<.05). This crossover interaction was because the N170 was more negative on the left for the WS group, and more negative on the right for the control group (see Fig. 6.3) The effects remained significant after normalisation (F(1,14)=4.2, P<.05).

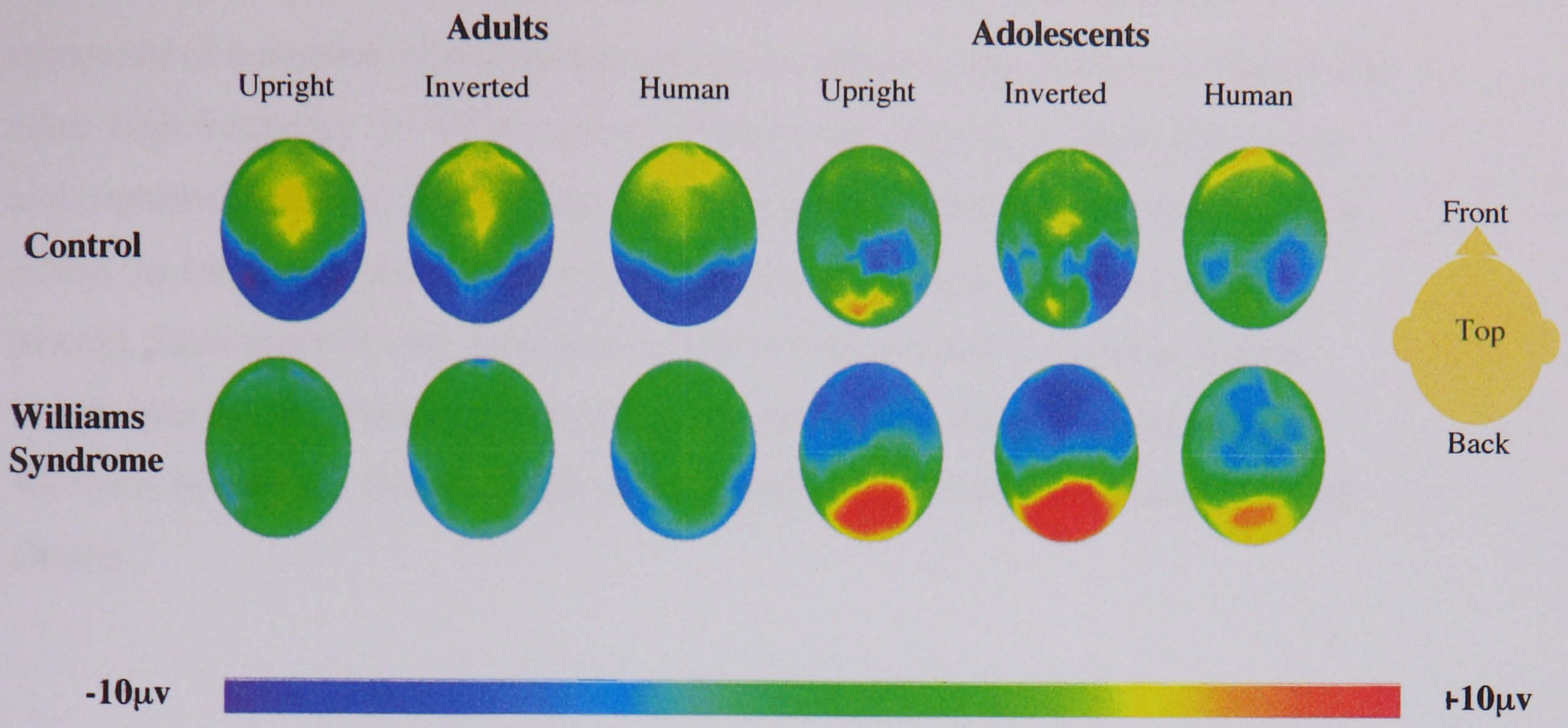


Figure 6.3 Topographic Scalp Maps showing Peak N170 to Monkey Face Stimuli

6.2 Role of Experience Summary

The results of Experiments 4A and 4B indicate that there is some normal differentiation in processing (at least in the latency domain) of human faces compared to monkey faces in Williams Syndrome. This is because inverted compared to upright monkey faces elicit only a very small increase in latency. This is no different to the specialisation of processing in controls. However, despite the specificity of processing stimulus orientation between categories, there appear to be no consistent differences between the waveforms across these categories (human faces, monkey faces, and objects) for people with Williams Syndrome. The further implications of these results will be discussed in the context of all other experiments in Chapter Eight.

Experiments presented in the current and previous chapters were designed to elucidate the functional characteristics of the WS cortical response to face stimuli. They focus on low frequency (< 30Hz) components of the Event-related Potential.

However, as discussed in Chapter Three, the electrocortical brain response is composed of a number of electrical frequencies. Much recent work has attempted to relate high frequency (≈ 40Hz) 'gamma-band' brain activity to visual processing and cognitive function. In particular, bursts of gamma-band activity are thought to reflect the binding together of spatially separate visual elements into a single percept. Such analysis may constitute an alternative method for gaining further insight into the abnormalities underlying the visual processing atypicalities in Williams Syndrome. Gamma band activity and 'binding' are the focus of the next chapter.

Chapter Seven

Binding

7 Binding

7.1 Five A - Gamma Analysis of Human-Face Study

7.1.1 Introduction

Behavioural data has suggested that the face encoding of people with Williams Syndrome fails to develop from depending on featural to depending on configural information. ERP evidence has been found from typical adult data for the specialisation of the neural systems responsible for the N170, but no consistent evidence of this kind was found from people with WS (although stimulus orientation processing does change with stimulus category). In addition, data from adolescents with WS suggest that all visual processing may follow a different developmental trajectory to that of controls. Electrophysiological abnormalities to faces may be particularly obvious in WS adults because face encoding is a highly specialised process, which in typical development probably modularises from general object processing neural networks. If the base from which face encoding develops is already atypical in being over 'featural' to all stimuli, then it is not just that the WS system fails to specialise for human face encoding, but that the whole visual processing system is already biased away from configural or global encoding.

In this chapter, the apparent difficulty in Williams Syndrome with integrating features together to compose whole objects or faces, is hypothesised to be related to 'binding' processes in the brain. Binding refers to how the brain combines together separately coded features of a stimulus to form a unitary representation. Here, however, it is applied specifically to the binding of spatially separate elements to form one object or scene. Different frequency bands of the human EEG can be separately analysed and have been associated with different aspects of brain function e.g. theta activity (3.5 – 7Hz) is associated with memory endoding and retrieval (Klimesch, 1996). A considerable amount of recent evidence from both cellular recording and scalp-recorded EEG has linked gamma-band neural oscillations to the

binding process (SInger & Gray, 1995; Muller, Bosch, Elbert, Kreiter, Sosa et al., 1996; Tallon-Baudry, Bertrand, Wienbruch, Ross & Pantev, 1997; Herrmann, Mecklinger & Pfeifer, 1999; Muller, 2000). Broadly, the claim is that the brain links aspects of the same stimulus together by the temporal correlation of neurons firing to that same stimulus. The frequency of this firing rate is around 40Hz (gamma band), and can be detected by EEG. For example, the perception of coherent objects has been shown to induce a peak of gamma activity at the scalp (Tallon-Baudry, Bertrand, Wienbruch et al., 1997), as has the perception of a whole face (Rodriguez, George, Lachaux, Martinerie, Renault et al., 1999). Even infants from around seven months of age show increased gamma activity to coherent illusory figures (Csibra, Davis, Spratling & Johnson, 2000).

The 'featural' hypothesis of WS visual processing can be re-formulated into a 'disordered binding' one. The strongest form of this hypothesis is that the apparent bias toward featural processing is caused by a disorder of neuronal synchronisation in the gamma range, such that spatially separate visual elements of the same object regularly fail to be coded as a single object, and are perceived as independent entities. In a study of EEG responses, this could be reflected in gamma bursting which is irregular, disorganised, or unaffected by the coherence of the stimulus. According to the data presented in the current thesis, any disorder of gamma bursting in WS should be particularly evident to face stimuli.

As a first step in investigating binding and gamma band activity in WS, adult data from Experiment One were re-analysed using a time frequency analysis to give a measure of induced gamma-band activity. In previous studies, the perception of upright and inverted 'Mooney' faces by normal adults has induced a gamma burst over frontal regions between 200 and 300ms (Rodriguez et al., 1999). The expectation was, then, that controls would show a similar frontal gamma burst that is larger to upright than to inverted faces. In addition, data from the adult autism group were also re-analysed. Autism could also be hypothesised to be a disorder of binding-related gamma activity, but no such disorders have hitherto been

investigated, so no other comparison to WS is available. Analysis of the autism data was undertaken to ascertain whether any potential abnormality would turn out to be specific to WS.

The proposal is that the binding abnormality would be specific to WS. Despite similar processing styles at the cognitive level, WS and autism have different behavioural outcomes. In WS visuospatial processing is very poor and slow, except for the processing of faces. The hypothesis is that a highly disordered system which is poor at processing the relationships between elements of a visual pattern has become expert at processing faces alone. This may be because of an excessive input of face information to the system throughout development. In contrast, people with autism are good and often fast at visuospatial tasks, except for the processing of faces. The hypothesis is that this object system is not inherently abnormal, but has not specialised for faces in the normal way. This may be because people with autism do not become expert at processing faces due to a lack of the necessary face input over development. In this case, then, the gamma induced to face stimuli whether upright or inverted should be the same, and look no different to that of other visual patterns.

Analysis was guided by three predictions:

i) Controls: Frontal gamma burst around 200-300ms, larger in amplitude to upright than inverted faces

ii) Autism: Frontal gamma burst un-modulated by orientation of stimulus

iii) WS: Gamma burst disordered and un-modulated by orientation of stimulus

7.1.2 Participants

Data that was off-line segmented and edited but not filtered, from the adult groups (WS, TD Control, and Autism) in Experiments One A and C, were used.

7.1.3 Methods

A time-frequency analysis of the data was performed[1] using a continuous wavelet transform. The Morlet wavelet was employed. This is a complex function of time, t, defined as:

$$w(t,f) = \frac{1}{\sigma_t\sqrt{\pi}} \exp\left(\frac{-t^2}{2\sigma_t^2}\right) \exp(2i\pi ft)$$

A set of wavelets with frequencies, f, covering the 21 to 60Hz range at intervals of 1Hz were used, and the parameter σ_t was defined as $\sigma_t = {}^{3.5}\!/_{\pi f}$.

To calculate induced activity the transform was applied to all EEG signals recorded at each channel across all individual trials. For evoked activity the transform was applied to the EEG signal after averaging across trials. The coefficients, $E(t,f)$, of the wavelet transform at a particular frequency, f, were calculated by convolving the EEG signal, $s(t)$, with the wavelet, $w(t, f)$, and taking the modulus of the resulting complex coefficients:

$$E(t,f) = |s(t) \otimes w(t,f)|.$$

$E(t,f)$ represents the time-varying amplitude of the signal within a frequency band centered on f. The mean value of $E(t,f)$ during the 100ms prior to stimulus onset was considered to be the baseline-level and was subtracted from $E(t,f)$. Average coefficients, for each subject, were calculated by taking the mean across trials, and grand average coefficients were calculated by taking the mean of the subject averages. In each case, $E(t,f)$ was also averaged across frequencies in the range 32 to 48Hz to provide a single, time-varying measure of the gamma-band activity. Channel groups were selected in frontal scalp regions on the basis of previous studies. Electrode sites are illustrated in Figure. 7.1 (c), and were chosen to include areas in which gamma bursting was maximal in all groups. Specific predictions of

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[1] Thanks to Micheal Spratling at the Centre for Brain and Cognitive Development for his help in performing this analysis

the data were analysed using Wilcoxon T tests, comparing gamma peak values to upright and inverted faces individually for each group.

7.1.4 Results

Prediction 5A(i): Controls: Frontal gamma burst around 200-300ms, larger in amplitude to upright than inverted faces

Results for the control group were very similar to those reported by Rodriguez and colleagues (Rodriguez et al., 1999). The gamma burst to pictures of real faces (see Figure.7.1) was located over frontal scalp regions and was consistent with previous results, i.e., larger in the upright compared to the inverted condition (Wilcoxon T = 2, Z= -2.24, P<0.05).

Prediction 5A(ii): Autism: Frontal gamma burst un-modulated by orientation of stimulus

There was a frontal gamma burst for the autism group which was similar to that of the control group. However, the burst did not change in size with stimulus inversion (Wilcoxon T = 4.2, Z=-.42, P=NS).

Prediction 5A(iii): WS: Gamma burst disordered and un-modulated by orientation of stimulus

Gamma activity for the WS group, as for the autism group, did not vary with stimulus inversion (Wilcoxon T = 4.5, Z = 0, P=NS). But Figure 7.1 (b) illustrates that averaged activity in the Williams Syndrome group was not organised into a clear burst in the same way as the other two groups; rather it was smeared across a longer time period. Inspection of individual plots showed no evidence in WS of any large amplitude bursts comparable to those seen in the control participants. However, the gamma activity amplitude over the whole period of 200 to 500ms was clearly different from baseline (Wilcoxon T=4, Z=-1.96, P<0.05). Thus, it was not the case that there was no gamma activity elicited in the WS response, but it was very different to the controls and other clinical group. There were also no differences in baseline activity between groups (TD:WS, Mann Whitney U= 32 , Z=0 ; TD:

Autism, U= 18, Z = -1.47, (P=NS)), indicating that the resting states were very similar and that it is induced frontal activity related to the stimulus that varies. The difference in gamma-band activity between groups was also not reflected in early

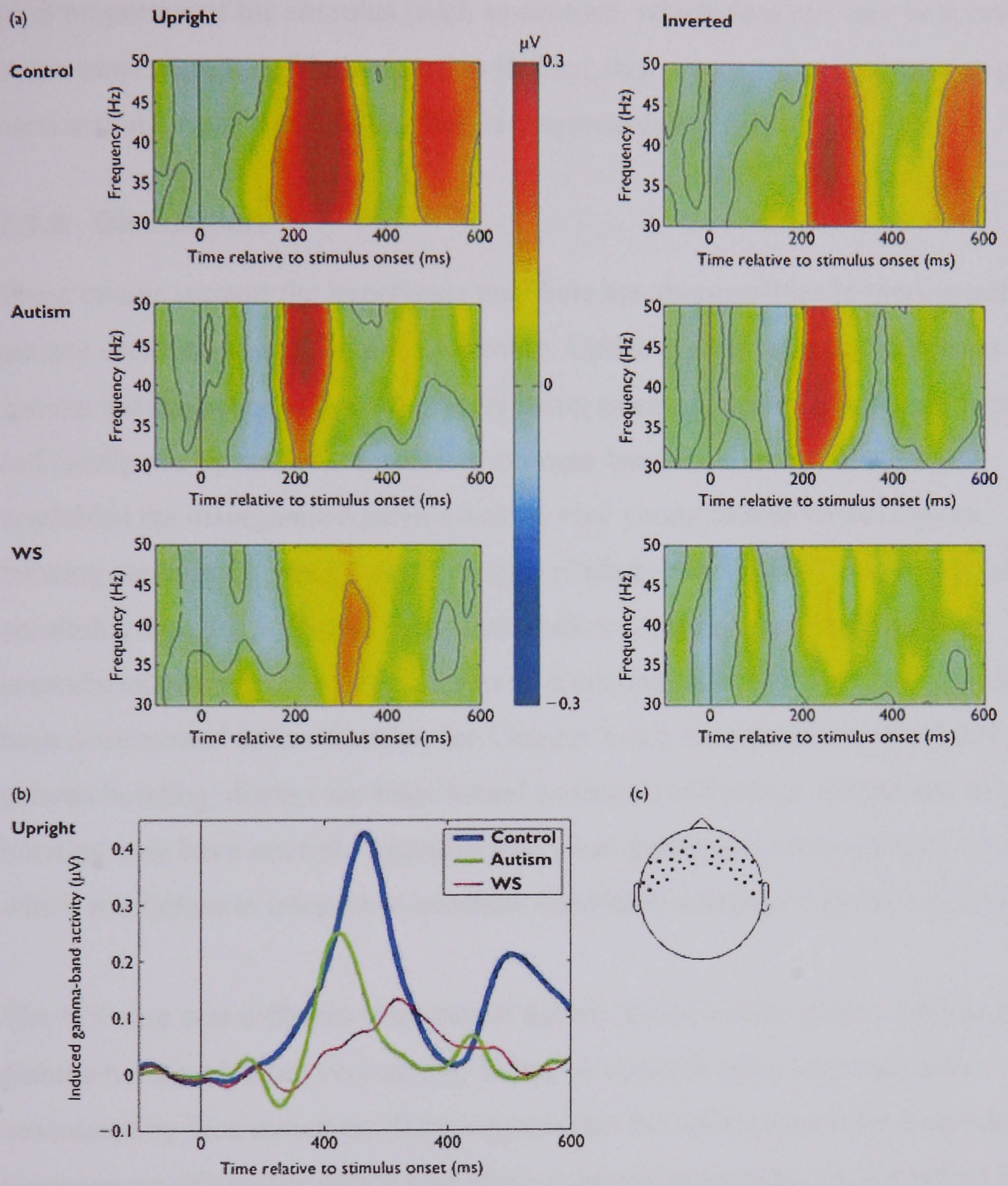

Figure 7.1 (a) Time-frequency plots showing induced gamma-band activity by orientation for each group, (b) Graph shows average gamma-band activity for each group in the upright face condition, (c) Top down view of the head with used electrode locations marked as black filled circles.

occipital phase-locked activity, analysis of which showed no significant differences (TD:WS, Mann Whitney U= 31 , Z=-1.05 ; TD: Autism, U= 27, Z = -.52, (P=NS)). This activity has been interpreted as the 'feature' burst that responds to the lowest-level properties of the stimulus (such as contrast, which does not vary with inversion of the same stimulus). The suggestion is, then, that it is specifically frontal gamma band activity, related to binding, that is catastrophically disrupted in WS.

7.1.5 Discussion

These results support the hypothesis that there are abnormalities in binding-related gamma oscillations in Williams Syndrome. Unlike typical adult responses, no clear gamma bursting occurred, with activity being smeared across longer time intervals and unaffected by stimulus inversion. Gamma-band EEG in the WS group resembled the disorganised pattern seen in very young infants before regular bursting emerges between 6 and 8 months (Csibra et al., 2000). This raises the possibility that, for Williams Syndrome, deficits in either neuroanatomical or neurochemical substrates (atypicalities of brain anatomy and chemistry have already been documented in the disorder, see Chapter Two), essential for task-related gamma bursting, disrupt the basic neural processes of binding. Disruption of gamma bursting may have multiple cognitive and visuo-perceptual consequences, one of which is a failure to integrate perceptual features to compose a global configuration.

The WS case was different from that of autism. In the autism group, binding-related gamma bursting looked very similar to that of controls apart from not being modulated by face inversion. This suggests that the differences in binding may be a consequence of another deficit elsewhere in neural processing, and/or reflect a difference in strategy or processing style with these stimuli. For example, it may be that the people with autism have a default preference for local processing but can process configural / global information if explicitly instructed to do so (Plaisted et al., 1999). One might expect in this case that, given instruction to attend to the whole face, people with autism would show normal task-related changes in gamma bursting. This is only one tentative hypothesis out of many possibilities, but could be

experimentally tested in the future. However, for the current thesis, the critical finding is that the autism responses were clearly organised into bursts, like controls but unlike those of the individuals with Williams Syndrome.

These results implicate a fundamental disorganisation in task-related gamma in Williams Syndrome. However, this is from re-analysis of data from an experiment that was not initially set-up to investigate binding or the gamma band. Faces are good stimuli to investigate visual perception differences in WS, but are not ideal stimuli to purely investigate binding differences. Most investigations of binding over typical development have investigated responses to simple black and white illusory stimuli, through which binding can be manipulated more directly. This was the goal of the next experiment.

7.2 Experiment Five B – Kanizsa

7.2.1 Introduction

The Kanizsa square stimulus in Figure 7.2 is composed of the same elements as the 'Pacmen' non-square. However, typically developing individuals perceive an additional illusory white square occluding four filled circles to the Kanizsa square stimulus alone (Kanizsa, 1978). For this reason, the Kanizsa figures have been used extensively to study the properties of the visual system, such as how it parses a visual scene into individual objects. Behavioural evidence, using habituation and preferential looking paradigms, suggest that infants from seven months of age are subject to the perception of the illusory figure (Bertenthal, Campos & Haith, 1980). This has recently been supported by electrophysiological research of gamma band responses in infants. Eight-month old infants showed an adult-like frontal gamma burst to illusory stimuli, which was absent for pacmen stimuli (Csibra et al., 2000). In contrast, infants of six months of age showed gamma activity that still discriminated between the two stimuli, but was different to that of adults in being 'smeared' over a longer time interval. The morphology of the gamma burst to faces

in WS seems, then, to be remarkably similar to the disorganised activity observed in typical infants of 6 months of age. It is possible that binding in WS never develops beyond this early stage.

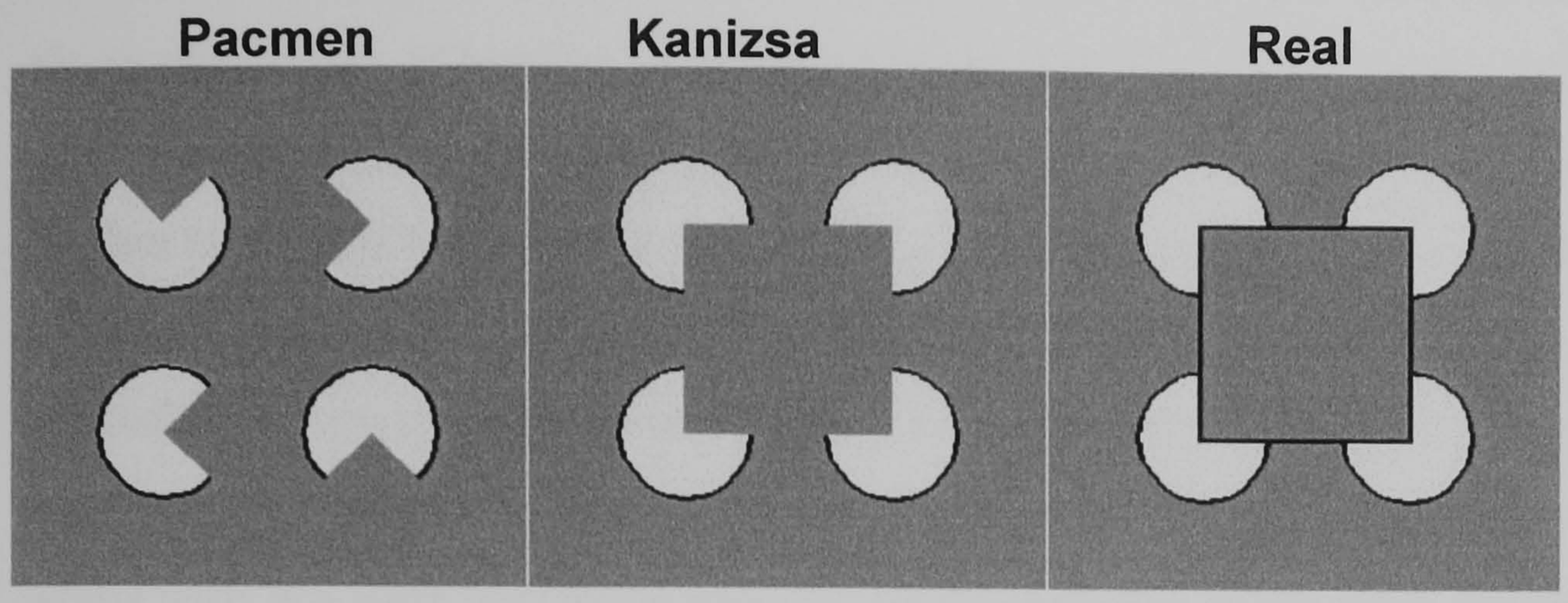

Figure 7.2 Kanizsa Stimuli

It has been argued throughout the current thesis that the N170 component in typical adults is enlarged by the configural encoding of visual information into a gestalt or 'whole'. If this is the case, then binding of the Kanizsa illusory square should be reflected in an increase in N170 amplitude compared to the Pacmen stimulus. This effect has been recently documented in two different studies (Herrmann et al., 1999; Herrmann & Bosch, 2001). In both studies, the Kanizsa square evoked a significantly larger N170 compared to the non-illusory figure. This supports the hypothesis that the N170 also to faces is, in part, enlarged by the requirement to bind spatially separate elements into a whole.

Only one study has documented the abilities of adolescents with WS to perceive illusory Kanizsa style figures (Wang et al., 1995). Wang and his colleagues used the Anomolous Contours Test (Hamsher, 1978) for which the participant is asked to trace or name the illusory shape. The WS group scored on average 12.3 (SD: 2.4) out of 15, which is slightly worse (though non-significantly so) than mental age matched controls with Down's syndrome. The task is easy for chronological-age and mental-age matched typically developing individuals. It is important to note that at least some of the time, people with WS can achieve binding, although not at the

level of typical controls. The question is whether this perception is subserved by the same neural systems and processes as for typical individuals.

The aim of the present experiment was to use Kanizsa stimuli to investigate the electrophysiology of binding in Williams Syndrome, at both low (under 30Hz) and gamma band (around 40Hz) frequencies. The stimuli were the same as those used by (Csibra et al., 2000). As can be seen in Figure 7.2 they consisted of a real square, a Kanizsa square and a Pacmen stimulus. The hypothesis considered WS as a disorder of binding. Given that normal adult-like activity (at both high and low frequencies) is achieved by around 7-8 months of age in typical development, adolescents and adults with WS were combined into one group under the assumption that any abnormality should be specific to the presence of the syndrome and not be significantly affected by age. The larger sample size also gives increased power to the analysis. With only seven participants per group (if split by age group), the experiment would be underpowered, due to the increased number of stimulus conditions (3 conditions in analysis) compared to the previous experiments. This constituted another change compared to the previous experiments. Experience from experiments Two and Three suggested that data collection from WS participants was difficult if stimuli were in greyscale or if they did not contain faces, because they were considered too boring. To combat this problem, colour face stimuli were randomly presented (25% probability) as targets to which the participant pressed a dummy button, and these filler data (uninterpretable due to motion artefacts) were subsequently discarded.

Analysis was guided by strong predictions at both low frequency ERP and induced gamma activity levels. The hypothesis for WS was that the number of elements, defined as the number of separate items, would determine the N170 amplitude rather than the presence of a gestalt. For example, the Kanizsa and Pacmen stimuli contain the same number of closed elements and should elicit a similar N170. In contrast, the real square contains more detail in being composed of lines as well as Pacmen.

Despite this, the real square should elicit for WS a smaller N170, because it comprises only one closed element. Predictions were:

ERP

i) Typical group N170 amplitude to Kanizsa square > Real Square > Pacmen.
WS group N170 amplitude to Kanizsa Square = Pacmen > Real Square.

Gamma

ii) Typical group: Frontal gamma activity organised into bursts.
WS group: Frontal gamma activity disorganised.
iii) Typical group: Bursts to Kanizsa and real square but not Pacmen stimuli.
WS group: Gamma activity no different to Kanizsa and Pacmen stimuli.

7.2.2 Participants

Participants were 15 individuals with WS (CA: 251(146) months) and 15 individually matched typically developing controls (CA: 253 (149) months).

7.2.3 Stimuli

The experimental stimuli used are shown in Figure 7.2. The face targets were the same as those presented in Experiment One. For each trial, a dark grey screen was presented with a flashing small light grey square in the centre for approx 500ms, before it was replaced by one of the experimental stimuli or face target for 307ms. These images were presented in random order at a 3.8 degrees of visual angle (from 75cm distance). The size of the illusory square produced from the Kanizsa stimulus was the same size as the real square at 2.3 degrees of visual angle. There was a 25% probability of any stimulus being presented. All presentation was in random order.

7.2.4 Procedure

For this experiment minor modifications of the procedure described in Chapter Three (Methods) were made. Participants were positioned in the sound booth behind a small table on which they were asked to rest their arms. On the table was a button box with one large red and one large blue button. The experimenter explained that

the red button should be pressed every time a face appeared on the screen. The hand used to press the button depended on the individual preferred use. They were asked to practise pressing the button several times without looking down at their hand as they did so. This was mastered immediately by all taking part. A practice session was then carried out with a helper or parent inside the testing booth to instruct and encourage where necessary, until the individual understood the requirements of the task (when they pressed only to all faces and not to other stimuli). This took less than one minute for all participants, except for the youngest male with WS for whom it took approximately four minutes (because he enjoyed pressing the button to every stimulus). The ERP data from all practice sessions were discarded.

Stimuli were randomly presented in four mixed stimuli blocks of 100 trials. After each block the experiment was interrupted and the participant offered a short break. The first 10 trials of each block after a break were discarded. The removal of this period meant that the recording was less noisy due to motion artefacts (while the participant regained a comfortable position etc.) and to the 'settling down' of the geodeisic net after such movement.

Time-frequency analysis of the gamma band was carried out in the same way as for the human-face analysis. Low frequency ERP analysis was carried out to test specific predictions of the data, using Analysis of Variance, with condition (3 levels) as a within subjects factor and Group (2 levels) as a between subjects factor. These analyses were followed up by t-tests where necessary for interpretation.

7.2.5 Results

Prediction 5B(i):

Typical group: N170 amplitude to Kanizsa square > Real Square > Pacmen.

WS group: N170 amplitude to Kanizsa Square = Pacmen > Real Square.

There was no main effect of group (F(1,28) =.24, P=NS), indicating that N170 activity overall stimuli was very similar for WS and control groups. However, there was a highly significant effect of stimulus (F(2,56)=12.67, P<.000). This was because there was no difference in the Kanizsa and Pacmen stimuli when compared directly (t(29)=1.14, P=NS), but both stimuli were larger in amplitude than the Real square stimulus (Kanizsa, t(29)=2.28, P<.05, Pacmen, t(29)=3.48, P<.05). The prediction was supported because the group by stimulus interaction was highly significant (F(2,56)=7.66, P<.001). This was because for the control group each stimulus elicited a different amplitude response such that Kanizsa > Real (t(14) = 2.6, P<.05) > Pacmen (t(14)=2.53, P<.05). In contrast, there was no difference between the N170 to the Kanizsa and Pacmen stimuli in the WS group (t(14)=.97, P=NS). In addition, the components elicited to both stimuli were significantly more negative that the Real (Kanizsa, t(14)=2.97, P<.05; Pacmen, t(14)=1.78, P<.05). These results are illustrated in Figures 7.3 and 7.4. There were no significant differences in latency across stimuli (F(1,28) = 1.36, P=NS) or group (F(1,28) =1.46, P=NS), and there was no interaction of stimulus latency with group (F(1,28) =.84, P=NS).

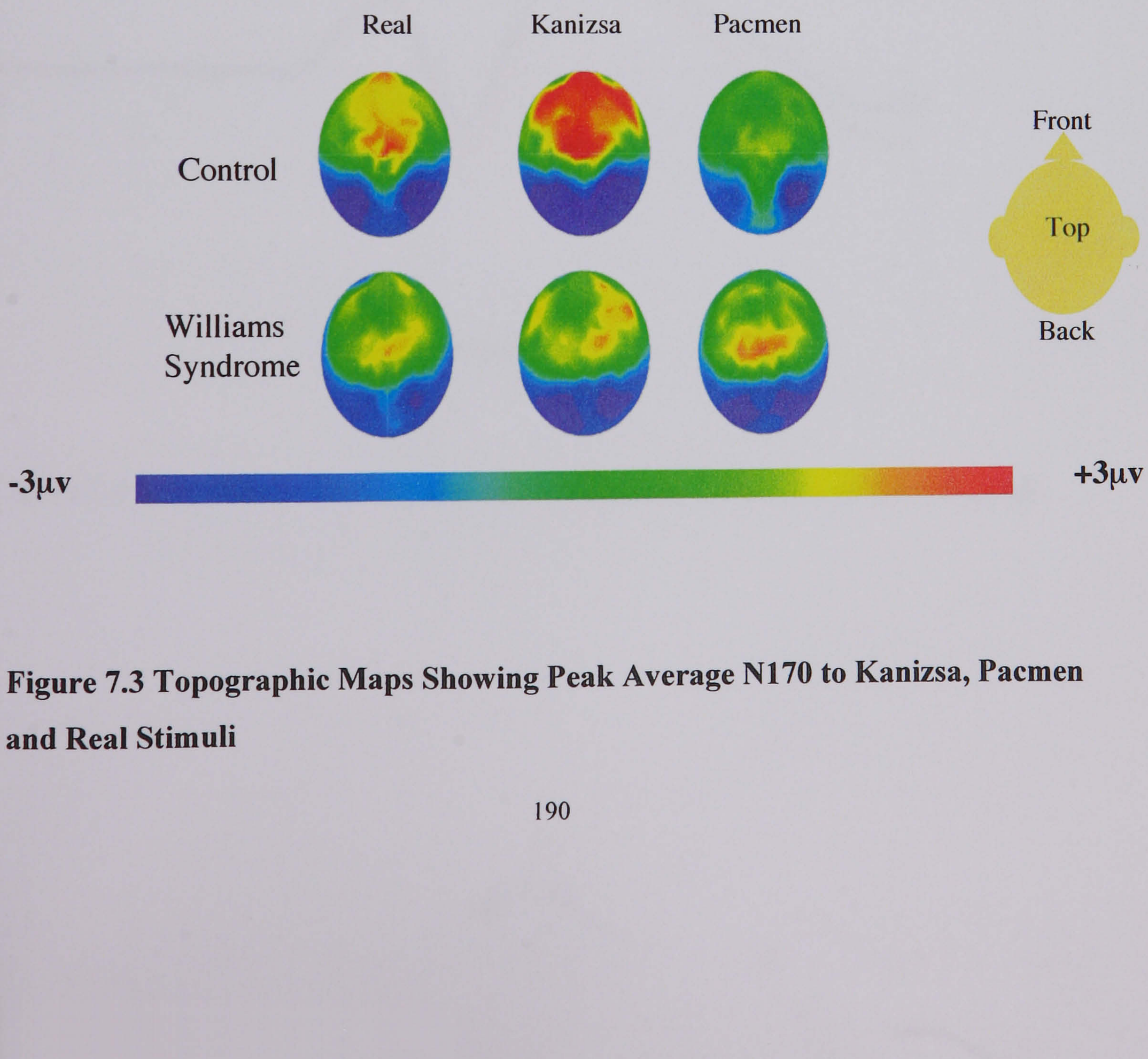

Figure 7.3 Topographic Maps Showing Peak Average N170 to Kanizsa, Pacmen and Real Stimuli

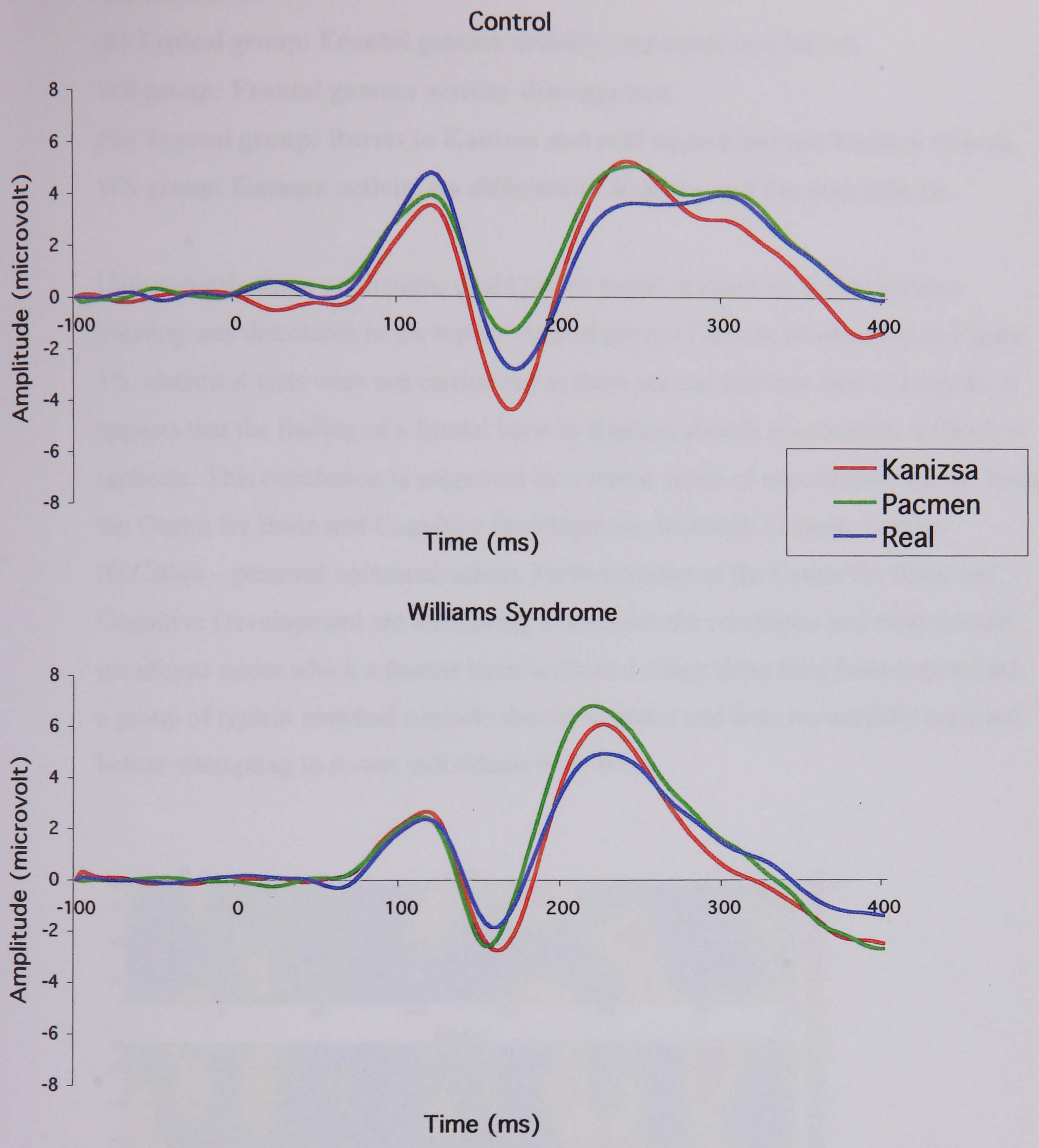

Figure 7.4 Waveforms showing activity to Kanizsa, Pacmen, and Real Stimuli

Prediction 5B

(ii) Typical group: Frontal gamma activity organised into bursts.

WS group: Frontal gamma activity disorganised.

(iii) Typical group: Bursts to Kanizsa and real square but not Pacmen stimuli.

WS group: Gamma activity no different to Kanizsa and Pacmen stimuli.

Unfortunately these predictions could not be tested because no frontal gamma bursting was detectable in the typical control group (This can be observed in Figure 7.5, statistical tests were not carried out as there was no relevant data to analyse). It appears that the finding of a frontal burst to Kanizsa stimuli is extremely difficult to replicate. This conclusion is supported by a recent series of unpublished studies from the Centre for Brain and Cognitive Development, Birkbeck College, London (G.Csibra – personal communication). Further studies at the Centre for Brain and Cognitive Development are attempting to pinpoint the conditions and experimental paradigms under which a frontal burst is elicited. Once these have been determined, a group of typical matched controls should be tested and data successfully analysed before attempting to re-test individuals with WS.

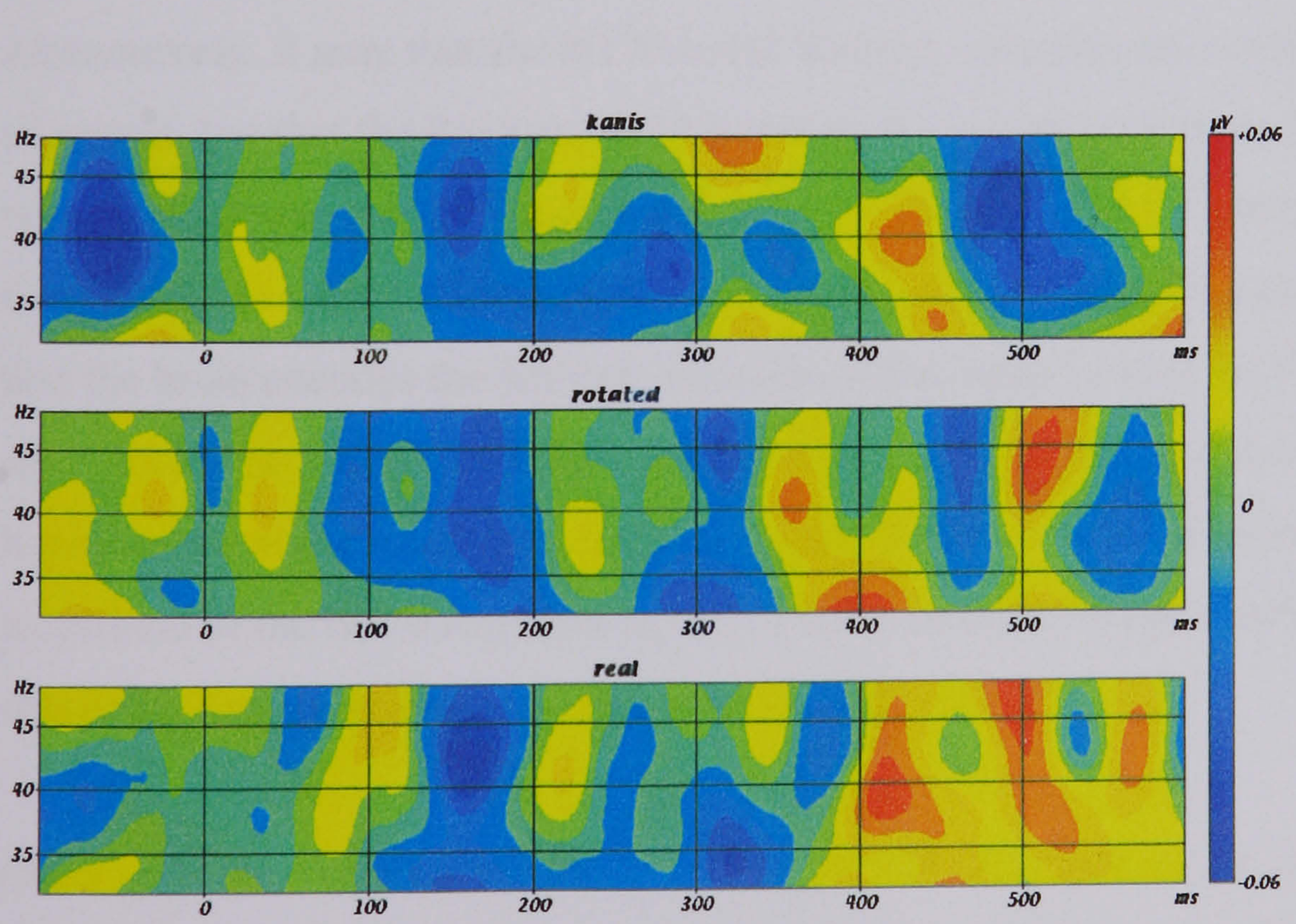

Figure 7.5 Time -Frequency plots showing Average Control Group Gamma Activity to Kanizsa Experiment (5B) Stimuli.

7.2.6 Discussion

The low frequency ERP results from Experiment Five provide the first experimental evidence for atypicalities in the binding of spatially separate visual elements by people with WS. In typically developing infants as young as eight months of age, the electro-cortical responses to 'Kanizsa', 'Pacmen' and 'Real' stimuli have been shown to be adult-like. Yet, despite the fact that the overall size of the N170 is normal, the differences between conditions are highly abnormal in WS. This supports the view that Williams Syndrome visual processing *develops* atypically (although an alternative is that WS is delayed from a point in infancy before six months of age, which has not yet been tested), as concluded on the basis of other experiments throughout the current thesis.

There are a number of possible explanations for the lack of difference between Kanizsa and Pacmen stimuli. The most conservative hypothesis is that the increase in activity to the Kanizsa stimulus is too small to be detected at the scalp. However, though possible, this appears unlikely since the overall size of the N170 is normal, and there is a significant difference between these stimuli and the Real Square. Alternatively, it may that the N170 to the Kanizsa stimulus does reflect the encoding of gestalt, but that the Pacmen N170 is enlarged to equal amplitude for a different reason. However, it is difficult to determine a property of the Pacmen stimulus that it does not share with the Kanizsa or Real square. A more parsimonious hypothesis is that the brain encodes the Kanizsa stimulus in the same way as the Pacmen stimulus, as if there is no additional effect of the illusory square. The results support the hypothesis that the number of separate closed elements to be encoded determines the amplitude of the N170 response in WS. This is an easily tested prediction which should be further investigated in future studies.

Other possible explanations for the results of this study rely on an abnormal allocation of attention in WS. It may be that people with the disorder focus on just one element of the visual scene. There is some evidence in young infants with WS for such 'sticky fixation' (Brown, 2000). However, if this were the case then one

might expect either similar or less activity to the Pacmen and Kanizsa stimulus compared to the Real stimulus. This is because the same elements are contained within all of the stimuli, but the Real square is also composed of additional elements. The current results stand in opposition to this prediction because the Pacmen and Kanizsa component was larger than that to the Real stimulus. The same argument holds for a serial versus parallel encoding style. If people with WS attend in a serial fashion to one element of the array at a time, then they would be unlikely to perceive the gestalt square, compared to typical individuals who are likely to attend in parallel. However, this cannot explain the difference between the N170 amplitude differences between stimuli because in this case, the Pacmen and Kanizsa N170 would be likely to be smaller than that to the Real square.

It is inaccurate to state that individuals with WS are unable to bind visual stimuli. Behavioural results reveal modest but not totally impaired performance on a task testing gestalt perception. It is more accurate to conclude that binding is i) different to typically developing individuals (at least those of six months of age and over), and ii) less successful than typically developing individuals. It is possible that the encoding of the illusory square, which enables some successful behavioural performance, simply happens later in the processing stream in WS compared to controls controls. This study, however, provides the first step in establishing the nature of the visual processing abnormalities in WS. It shows, like the preceding studies presented in the current thesis, that the early perceptual processing stages and not just later 'construction' stages, are atypical in the disorder. Future ERP studies should attempt to further determine the typical and atypical functional characteristics of the WS N170 response, and to investigate where in the processing stream the encoding of the illusory square may occur. Behavioural studies should also be designed, measuring accuracy and reaction time, to directly test binding both of form alone (binding within cortical area) and eventually of form with other visual attributes such as colour (binding between cortical areas).

7.3 Chapter Seven Summary

The results discussed in Chapter Seven present an intriguing picture of the visual processing abnormalities in Williams Syndrome. Both induced gamma analysis of the human-face experiment, and low frequency ERP analysis of the Kanizsa experiment, support the characterisation of WS as involving abnormalities of visual binding. Previous studies have documented the 'featural processing' style of people with WS, but none have attempted to provide an explanatory account of such a style, or an investigation of the possible brain basis. The studies presented here comprise a preliminary attempt to do both.

Behavioural studies have found that people with WS are able to encode individual elements of visual scenes, but appear to have difficulty with integrating these elements into a coherent whole. This becomes, manifest in tasks where individuals are required to code the spatial relationships between visual features (Deruelle *et al.*, 1999). The analysis of activity in this gamma frequency band in WS suggests severe disruption of neuronal synchronicity. Activity is not organised into high amplitude synchronous bursts as it is for typically developing individuals, but rather smaller increases in amplitude which appear broad and 'smeared' in appearance like those of very young infants. Both these cortical responses, and those at lower frequencies support the notion that WS impairs integration. The interaction between low and high frequency processing is not known. In addition the potential interactive effects over development can only be speculated to be catastrophic for visual processing in the WS case. The atypical binding hypothesis of WS, presented for the first time here, should be investigated, and the current effects replicated, before further conclusions can be drawn. The possible relationship between binding abnormalities and the development of face encoding in WS will be discussed in the next chapter.

Chapter Eight

Conclusion

8 Conclusion

8.1 Introduction

At the broadest level, the experiments that comprise the current thesis demonstrate that, contrary to previous claims, face processing is not 'spared' in Williams Syndrome. Not only is face encoding atypical in the WS endstate, but it also follows a different trajectory of development. In addition, the studies provide evidence that the WS visuo-spatial impairment is not merely confined to a deficit of 'visuo-construction' but is also present very early in perceptual processing. However, the aim of the current chapter is to attempt to go beyond characterisation in order to start to *explain* the state of visual encoding in WS. The design of the experimental studies was driven by a new approach to the imaging of developmental disorders described by Johnson and colleagues (Johnson et al., In Press). This approach is based on an 'Interactive Specialisation' (IS) view of brain development. The success of the endeavour and the use of the IS approach in interpreting the results will be assessed in the current chapter. Finally, implications for the future imaging of developmental disorders will be discussed, and further studies suggested.

8.2 Modularisation of Function

The results of the first three experimental chapters confirm that face processing is not an 'intact' genetically specificied module in Williams Syndrome. Further, they imply that specialisation of early brain mechanisms for the processing of faces over other visual stimuli is abnormally lacking. These data do not suggest that face processing is an 'impaired' module in WS, but that progessive specialisation of the early visual processing system (which probably 'modularises' face processing in the typical case), follows a highly atypical trajectory in the disorder and the consequence is a failure to modularise even in the WS endstate.

The study of the WS endstate indicated overall: a. that the electrophysiological correlate of face encoding (N170) is abnormal in morphology and probably

lateralisation; b. that the early encoding system (indexed by N170) is less specialised for upright faces compared to other upright stimuli than that in controls; c. that unlike the N170 of controls, the WS N170 amplitude does not vary with face inversion. The only normally face sensitive characteristic of the WS N170 is the large increase in latency with inversion. This modulation is smaller with the inversion of monkey faces, and absent with the inversion of cars. Data for both of these comparisons were very similar to those of controls. Latency, then, is highly sensitive to inversion of particular categories in WS. The question is how this might be explained.

The modulation of N170 latency by inversion of a face stimulus has been explained in a number of ways in the typical adult literature (Rossion et al., 2000). One hypothesis is that latency changes represent differences in 'difficulty'. The later the peak the more difficult was the encoding. However, what exactly does difficulty mean? Why is a face more difficult to encode when upside down, and an inverted car is not? It is likely that the difference is in the nature of the encoding that typically takes place for the upright stimulus. Faces are thought to be encoded by typical adults primarily by configural properties, whereas other visual stimuli are usually encoded in a piecemeal fashion (see Chapter One). Most experience is with upright face exemplars; hence, when a face is inverted the encoding of configural information is disrupted. This may also be because the stimulus is mentally rotated, and it is difficult to rotate multiple features simultaneously to maintain configural information. In contrast, the encoding of features is much less disrupted by inversion because individual features are easy to mentally rotate. The reason that stimuli such as cars are less affected may be because they are not encoded using configural information. An alternative to this hypothesis is that fewer features of non-face objects are encoded compared to faces, and therefore the mental rotation of these stimuli is easier.

The WS results show that N170 latency increases normally with the inversion of faces. It is also unaffected, like that of typical adults, by the inversion of a car

stimulus. If the 'number of encoded features' hypothesis were correct then it would indicate merely that people with WS are normally affected by an increase in mental rotation load. However, this seems unlikely to be the whole story. The role of mental rotation load is still unclear in behavioural research on the face processing of typical adults, though the role of configuration has been shown to be key (Leder & Bruce, 2000). If the disruption of configural information is also the cause of the N170 inversion effect then the WS latency results are difficult to interpret. Behavioural results indicate that people with WS are very poor at encoding configural information from faces and from other objects. The amplitude results of Experiment Five (Kanizsa) also suggest that the WS N170 is less sensitive than typical adults to such information. Both would predict an abnormally attenuated N170 inversion effect.

It is the case that an abnormally attenuated (absent) face inversion effect was found for the amplitude of N170. An increase in amplitude with inversion has, to date, been found for every typical adult tested using these face stimuli*. Yet the effect was absent for every WS individual tested. There are at least three possible reasons for this finding: first, that there was an increase in activation but it was too small to be detected at the scalp. This may be related to the small size of the deflection in WS, where a similar ratio increase in size compared to controls would be too small to show up as a significant difference; second, that the amplitude effect is severely developmentally delayed in WS. Developmental research has shown that the amplitude inversion effect starts to appear later than the latency effect and continues to mature into adulthood, well after the latency effect has matured (Taylor, Edmonds et al., 2001). This was confirmed in the data from typical adolescents in Experiment One-B, for whom there was also no inversion amplitude effect. However, a 'delay'

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* but, it should be noted that such modulation has not been found for every set of face stimuli reported in the literature e.g. Bentin et al. (1996). It is unclear what the determinants of such an effect are, and why it would be so robust with one stimulus set and not another. One possibility is that it reflects the difference between studies based predominantly on university undergraduates for whom the effect might still be expected to be immature, and those that include older adults amongst the sample.

hypothesis may be less convincing because overall the results of Experiment One-B indicate that the WS waveform undergoes a different trajectory that is unlike anything seen in typical development to date; third, that the amplitude increase reflects an increase in neural activation, or a long lasting attentional negativity, in the typical case which does not occur in WS. A possible explanation is then that the degree of WS neural activation is unmodulated in response to difficulty, or that the structural encoding of inverted compared to upright faces is less difficult for adults with WS than typical adults. Clearly, the latter fits well with results documented in the behavioural literature.

The fact that the peak of the N170 in Williams Syndrome is delayed by the inversion of faces, and the stimulus sensitivity of this effect, is difficult to explain on the basis of behavioural, amplitude, and Kanizsa results. However, there are a number of possible interpretations. As mentioned above, the face inversion latency effect is very early to reach maturation in the typical case compared to the face inversion amplitude effect. So the WS waveform may reflect the working of a partially specialised system. However, as mentioned above, the atypical trajectory of WS development through adolescence may militate against this conclusion.
Alternatively, a mental rotation explanation could be invoked, such that people with WS attempt immediately to mentally transform the upside down face to an upright position. However, the question is why this would not occur also for cars. The 'mental rotation' hypotheses alone cannot account for the lack of inversion effect for car stimuli. However, it is entirely possible that cars hold very little interest for people with WS: perhaps an abnormal increase in the N170 latency to inverted compared to upright cars would occur if these stimuli were of particular interest to these individuals. This would be in contrast to faces (of any kind) which appear unusually attention grabbing for them. Further work is needed to find out what does determine why the N170 latency of people with WS is sensitive to differences in stimuli when the N170 amplitude is not.

The ideal solution to determine the state of the WS visual encoding system might be to combine the current ERP results with those of an fMRI study. This could determine whether activation increases, or progressive localisation (for example of the Fusiform Face Area) is like that of typical individuals. However, this kind of experiment is currently difficult with people with WS. The high anxiety level and hyperacusis typical of individuals with the disorder would render such an experiment unethical (in the author's view). Instead, it may be that behavioural and ERP experiments should focus on the progression of face encoding over development from infancy. This could help to determine whether the starting state in WS is equivalent to that of typically developing controls, or whether even this is atypical. Further behavioural experiments could also attempt to determine the exact nature of the 'configural' deficit. For example, what is the spatial distance, between the elements of a pattern, at which configural sensitivity breaks down in WS? Is this a static distance which is true for all stimuli? These are questions which should be investigated for both faces and other visual stimuli.

8.3 Perception

The results of all studies presented in this thesis suggest that correlates of early visual processing are atypical in the WS endstate, and follow an atypical trajectory at least through adolescence. In the WS literature a crude distinction is made between visuo-construction, and all processing that occurs before construction, which is termed 'perception'. This definition of perception is a wide and also includes components such as attention. As discussed in Chapter Two, some (Pani et al., 1999) have argued that these early stages are 'intact' in WS and it is only visuo-construction that is impaired. However, the results contained within all experimental chapters presented here militate against the conclusion that 'perception' is intact. Even within the first 200 ms of visual processing, there are significant and informative differences between people with WS and typical controls.

The gamma-band analysis and Kanizsa experiment of Chapter Seven attempted to investigate the nature of perceptual differences in WS, and proposed a new 'atypical

binding' hypothesis to explain visual processing in the disorder. The low frequency Kanizsa results support the hypothesis that early encoding is more piecemeal in WS. The results were strikingly atypical, compared to controls for whom the condition effects are mature even in infants as young as six months of age. A necessary future step is to test WS infants using the same Kanizsa stimuli, to confirm that the abnormality is also present early in life. Currently, there can only be speculation about the effect that a low-level abnormality of this nature may have on the development of the visual processing system in WS. The same is true of the consequence of the atypical binding-related gamma bursting which was evident to human face stimuli. Both sets of results may be crucial to the understanding of the WS visuo-spatial impairment, and for this reason the gamma results require replication with a larger WS group. Also necessary is replication with different stimuli, for example the visual search stimuli (described below) used by Tallon-Baudry and colleagues (Tallon-Baudry, Bertrand, Delpuech & Pernier, 1997). Behavioural studies designed to directly test behavioural binding should accompany these endeavours.

8.4 Previous Hypotheses

Several hypotheses previously proposed to account for the WS profile of visuo-spatial cognition were discussed in Chapter Two: 'visual deficit', 'right hemisphere', and 'dorsal stream'. The data presented here suggest that a sensory-visual deficit (e.g. strabismus, visual acuity loss, amblyopia, or reduced stereopsis) does not need to be evoked to account for the typical WS profile. They also suggest that the 'intact ventral' versus 'deficit dorsal' distinction does not hold. Face processing is a classic example of ventral stream functioning and yet the findings presented here have shown it to be far from 'intact'. This hypothesis requires refining to take into account differences in the growth of the developmentally disordered brain. It may be that dorsal stream development is more atypical than the development of the ventral stream, but it is not the case that the dorsal stream alone is impaired. A similar conclusion may be drawn for the right hemisphere hypothesis. It is interesting to note that when typical adults show lateralisation for face encoding, it is usually

predominantly in the right rather than the left hemisphere. This is related to the broad claim from neuropsychological research that 'features' tend to be processed more in the LH, and 'wholes' more in the RH. It is the case that for studies in the current thesis lateralisation (when it occurred) for the WS group was always over the LH rather than RH. Clearly, this finding could lend some weight to the hypothesis. However, it is unclear why the WS brain would be more active in the LH, rather than the RH, since it is still unclear why lateralisation for face processing occurs in typical development. One hypothesis is that the RH is first to receive subcortical 'face' information, and is also faster to mature (de Schonen et al., 1993). The study of subcortical versus cortical face processing in WS infants, for example using visual hemifield studies such as those (described in Chapter One) of Simion and colleagues (Simion, Valenza, Umilta & Dalla Barba, 1995) may then help to explain the WS results.

8.5 Syndrome Specificity

The WS adult response to face stimuli was compared to that of adults with autism, in analyses of both low and high frequency bands. Unlike the WS group, the autism group showed no abnormality of N170. Gamma bursting also looked relatively normal except that the amplitude of the burst was abnormally un-modulated by stimulus orientation. Despite the purportedly similar featural processing 'style' at the cognitive level, the electrophysiological responses of individuals with WS are different from those of people with autism. This is important for two reasons. First, similarities found at one level of analysis, behavioural, cognitive, or neural, do not necessarily correlate with similarities at other levels. Second, the electrophysiological abnormalities of people with WS (i.e. attenuated N170 and disordered frontal gamma bursting) may be syndrome specific, and potentially could be used as 'markers' for the disorder. Clearly, further work should be carried out to replicate the WS effects on different and larger groups. Also necessary is an investigation of the electro-cortical responses to visual stimuli of people with other developmental disorders. For example, abnormalities of visuo-spatial cognition have been documented in both Fragile-X syndrome (Cornish, Munir & Cross, 1998;

Cornish, Munir & Cross, 1999), and Turners Syndrome (Silbert, Wolff & Lilienthal, 1977). A comparison across disorders is necessary in order to validate the syndrome specificity of the WS electrophysiological abnormalities, i.e., as markers of the atypical development of WS alone.

8.6 Approaches to Imaging Developmental Disorders

As discussed in the Preamble, most imaging studies of developmental disorders are driven by a maturational approach with three assumptions. These are that a cognitive or behavioural weakness in an individual with a developmental disorder will be caused by a *deficit* which is *localised* and is *static* across age. The studies presented in the current thesis were driven by the Interactive Specialisation Approach which postulates that the brains of those with developmental disorders may develop differently from embryogenesis onwards. The assumptions are that neural systems underlying both weakness *and* strengths in developmental disorders may have developed differently from controls. IS is a form of neuroconstructivism which, unlike many hypotheses of brain development, does not assume that progressive localisation of function is a necessary consequence of progressive specialisation.A focal deficit is unlikely, with development being interactive both between the organism and its experience with its internal (brain) and external (the world) environment.

The IS approach was translated in this thesis into the study of a behavioural strength in WS. As predicted, there were abnormalities even within this relatively successful domain of performance. It was investigated using a technique able to measure the temporal dynamics of neural processing, as opposed to one with high spatial resolution. The thesis culminated in the study of (and new hypothesis about) differences in inter-regional interactions, rather than of deficits in single structures or single pathways (see also Friston & Price, 2000). Data was obtained from several age groups to examine whether people with WS show the same pattern as observed at younger ages during typical development. It was found that they did not. In addition, cross-syndrome comparisons were made in order to determine whether a

similar cognitive style - 'featural processing' - was caused by the same neural processing. It was shown that WS could be dissociated from at least one other disorder at the electrophysiological level.

It is hoped that the studies contained within the thesis are a convincing advocate for the use of the IS approach in guiding and interpreting imaging studies of developmental disorders.The IS approach implies that the search for gross focal abnormalities in discrete brain regions is unlikely to be successful, but this does not mean that the imaging of such disorders is a pointless mission. If there are subtle but widespread abnormalities in the developing brain then different patterns of interaction between cortical regions may result in atypical trajectories of development. The imaging studies presented here have produced some evidence both of atypical patterns of regional interaction in the cortex of adults with WS, and of an atypical developmental trajectory across adolescence. They have also shown that the fine examination of a supposedly 'preserved' area of cognitive and behavioural functioning can be informative about the course of abnormal development as can domains of grossly abnormal functioning.

8.7 Future Studies

There are a number of analyses that did not fall within the scope of the current thesis for reasons of time and resources. For example, gamma-band analysis is time consuming and it was unfortunately not possible here to compare gamma-bursting of the adolescent groups with each other or the adult groups. In addition, it was not possible to analyse gamma bursting to car or monkey face stimuli. All of these analyses are planned for the future. A different kind of analysis is also planned. This is to directly investigate 'coherence' between activity at different electrode sites on the head. Coherence is a statistical measurement of the correlation between two signals as a function of the frequency components they contain (Shaw, 1984). It has been used recently to map interactions between different cortical areas in typical face processing (Rodriguez et al., 1999), and could eventually be used to map abnormal region-to-region interaction in WS. Coherence analysis could test, for

example, whether there is a failure of synchronicity of gamma band oscillations between frontal and occipito-temporal regions in addition to the failure to produce regular stimulus-locked bursting in frontal regions to face stimuli in WS.

A number of future studies have been suggested throughout the thesis. However, of these, two lines of study are currently being developed. The first is to replicate abnormalities of gamma bursting on a larger group of individuals with WS, using experiments designed to directly test binding. One example of such an experiment is that of Tallon-Baudry (Tallon-Baudry, Bertrand, Delpuech & Permier, 1997), where the same degraded stimulus is perceived either as a bound, meaningful object, which induces a gamma burst, or as random dots, which evokes no gamma burst, depending on previous exposure to the non-degraded stimulus . Behavioural work will also be used to establish whether individuals with WS are able to achieve such top-down modulation of perception, by asking participants to trace the bound shape. The prediction is that gamma bursting will be disorganised in the same way as that to human faces, and like that to human faces will also show no modulation with 'binding'. If these effects are replicated, then the next step will be to investigate another domain of sensory function which requires binding, such as auditory perception. If the results described in Chapter Seven can be attributed to abnormalities of neurochemical substrates, then it is possible that the abnormalities of inter-region synchronicity will effect development in other domains (although neurochemical abnormalities are not necessarily domain-general). In this sense, a disorder of synchronous oscillatory brain activity may eventually be helpful in explaining the development of many different cognitive abnormalities in WS.

The second line of research is to further investigate gamma bursting in autism. An autism group was used in the current thesis only as comparison to the WS group. However, autism is a disorder which demands further investigation in this area. Particularly of interest is to investigate people with autism as 'super-binders'. Under some circumstances, and in contrast to the prediction of the 'weak central coherence hypothesis' (Frith, 1989), people with autism are significantly faster than CA

matched individuals at identifying targets uniquely identified by the combination of features (O'Riordan, Plaisted, Driver & Baron-Cohen, 2001). In the human face data-set presented in Chapter Seven, there was an (albeit non-significant) indication that the peak gamma bursting of individuals with autism occurred at a slightly earlier latency than that of controls or of individuals with WS. The aim is to investigate this effect using a larger pool of subjects, and to attempt to correlate speed of behavioural binding with the peak latency of gamma burst.

8.8 Final Conclusions

In the current thesis, the Interactive Specialisation Approach was usefully employed to investigate face perception in WS. The results show that face processing in WS is not 'spared', as some others had previously claimed. In addition, the results show that visuo-perception, and not just visuo-construction, develops differently in the syndrome. Finally, evidence was found to support a new 'abnormal binding' hypothesis which aims to explain the nature of the visual processing style in WS, and to relate it to abnormalities of the underlying neural processes. Disruption of synchronous oscillation in the gamma band may be eventually turn out to be the neural basis of the WS visuo-cognitive profile.

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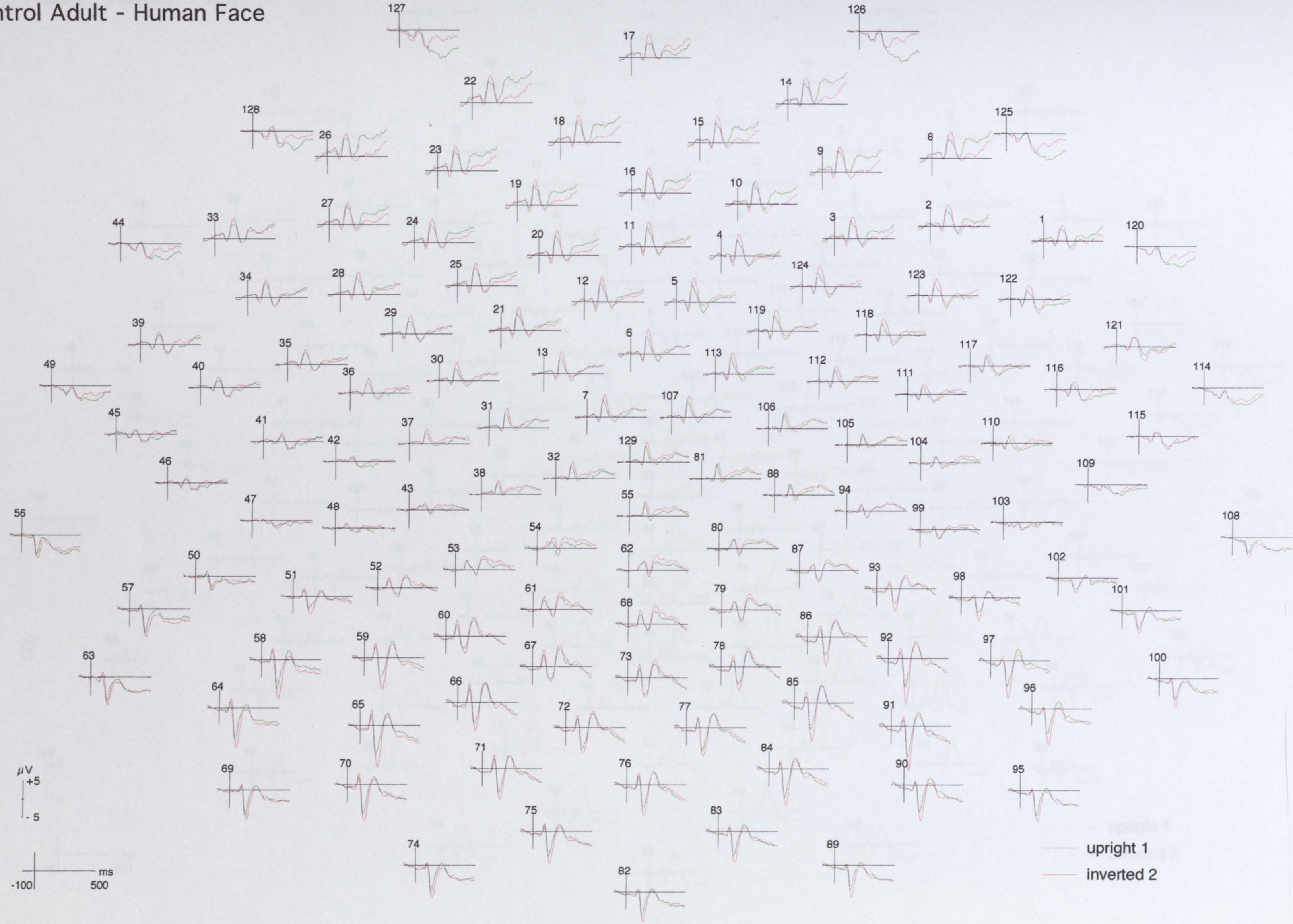
Appendix 1

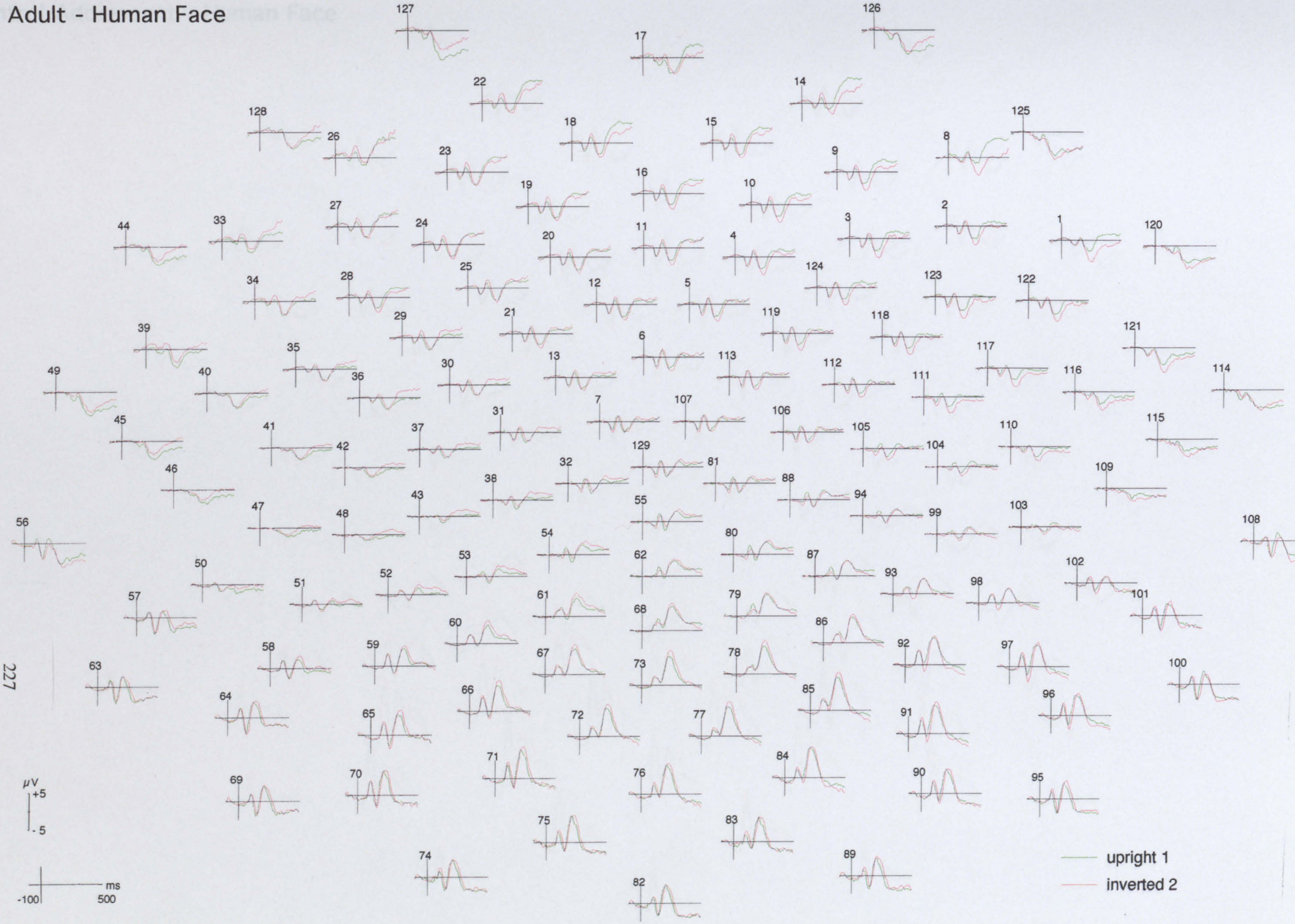
Human-Face

Grand-Average Scalp Maps

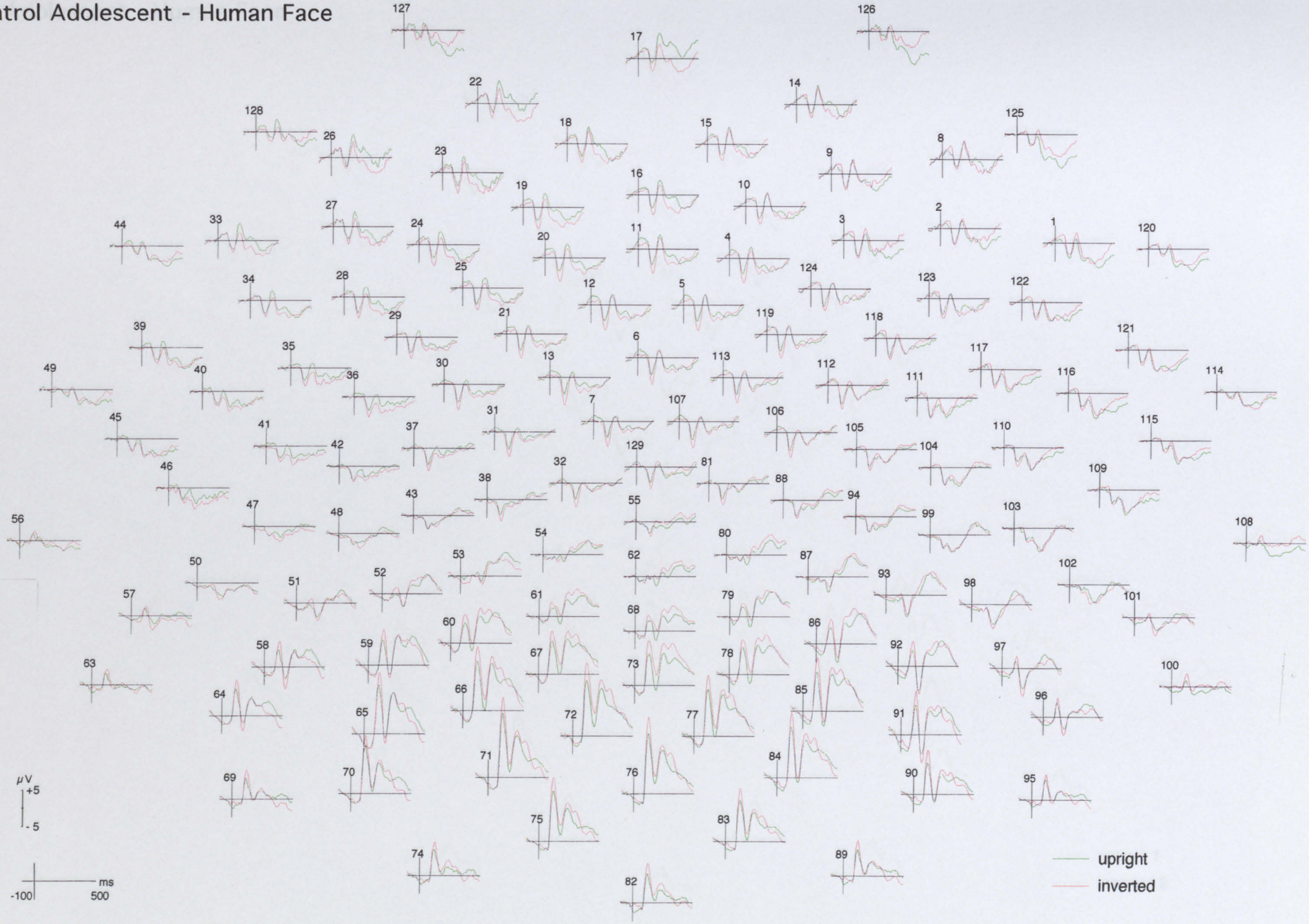
Control Adult - Human Face



WS Adult - Human Face



Control Adolescent - Human Face



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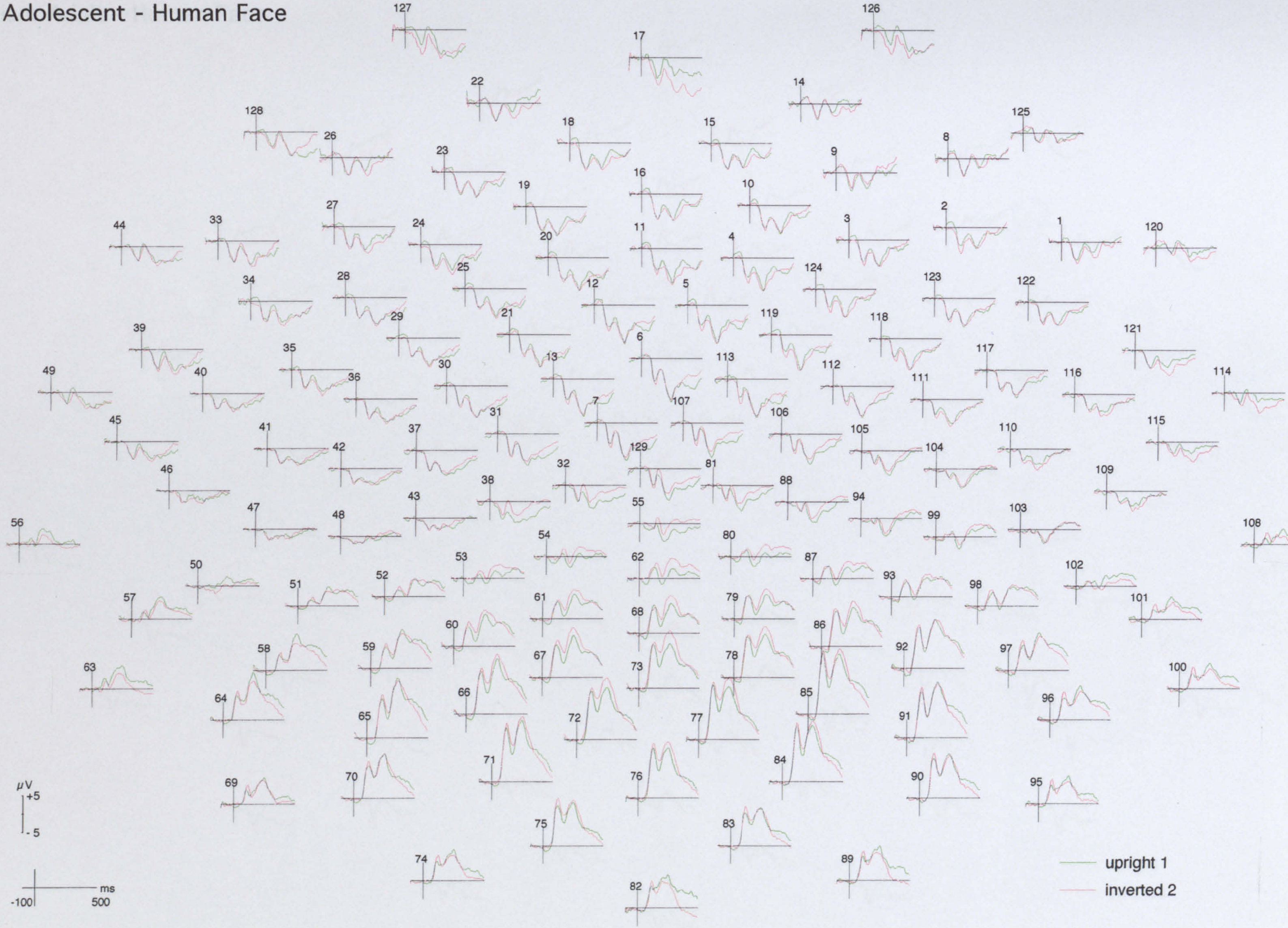
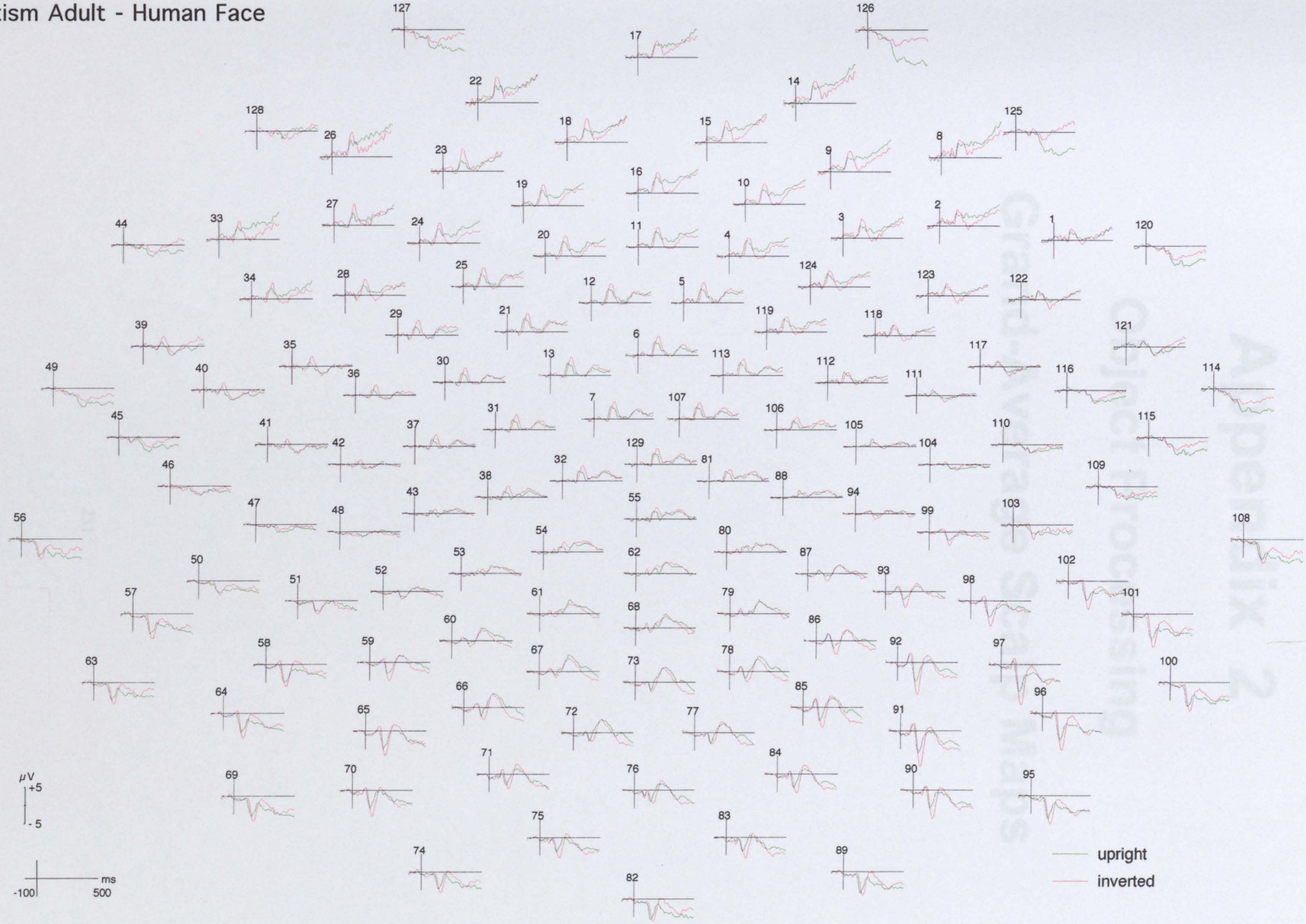


Autism Adult - Human Face

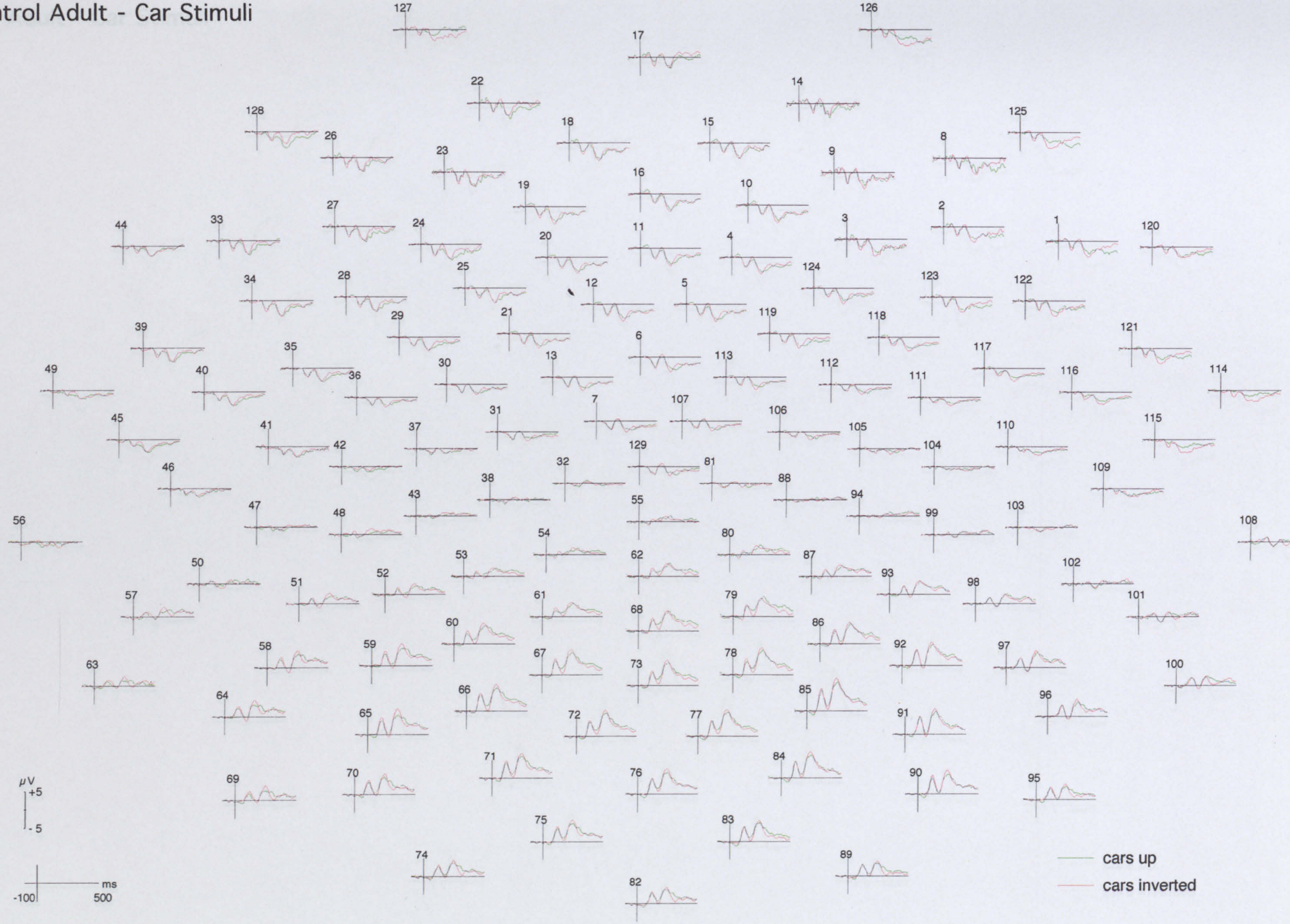


Appendix 2

Object Processing

Grand-Average Scalp Maps

Control Adult - Car Stimuli



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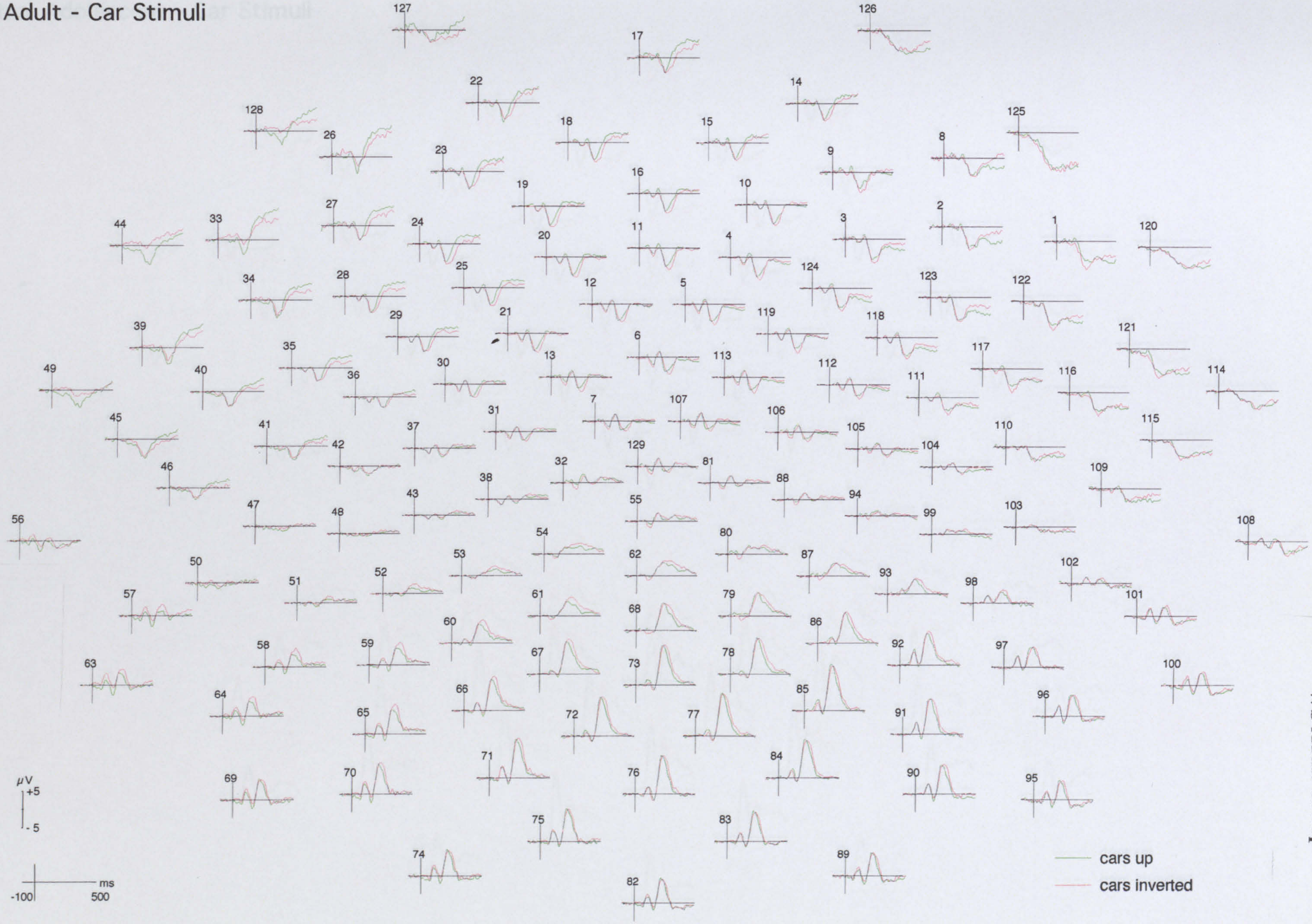
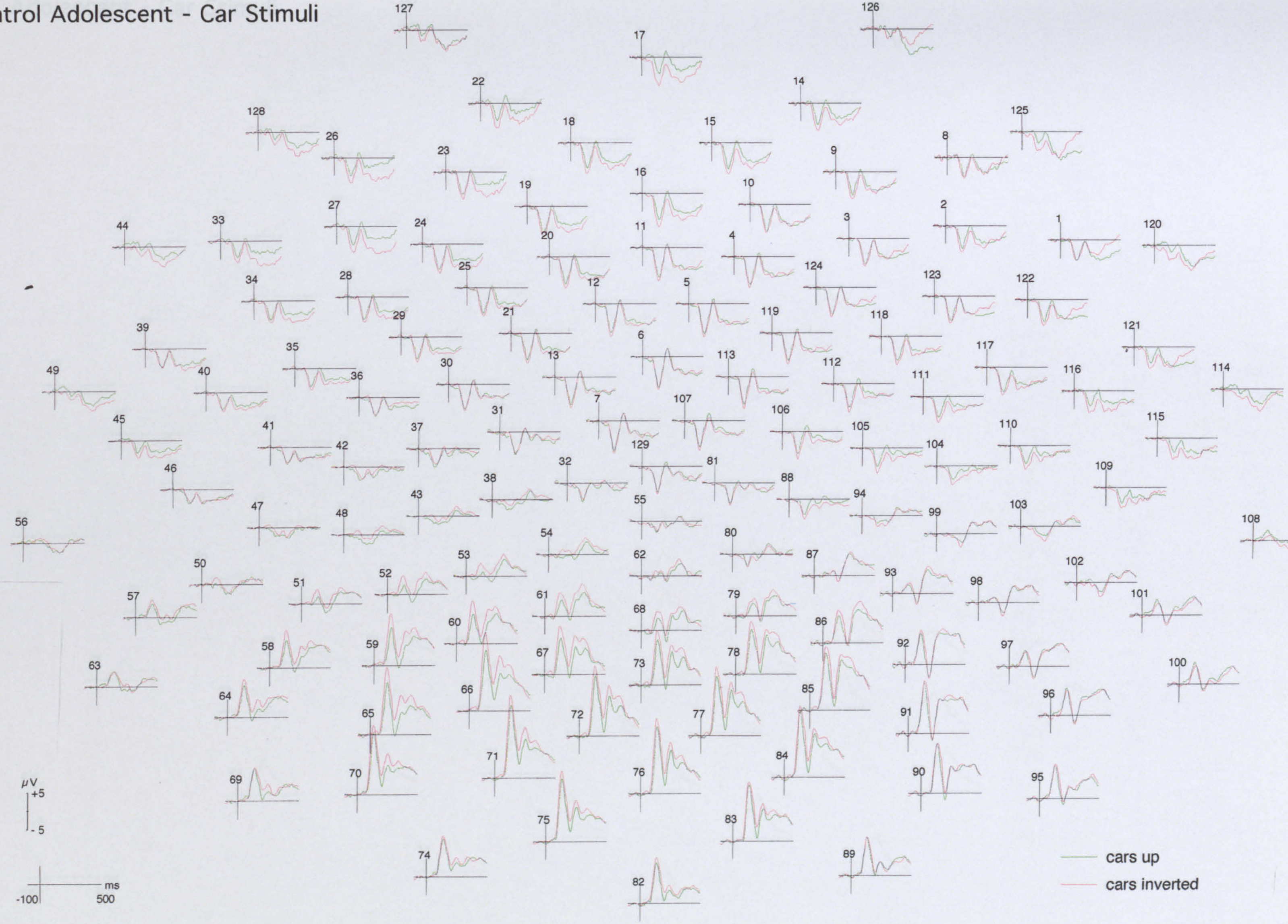
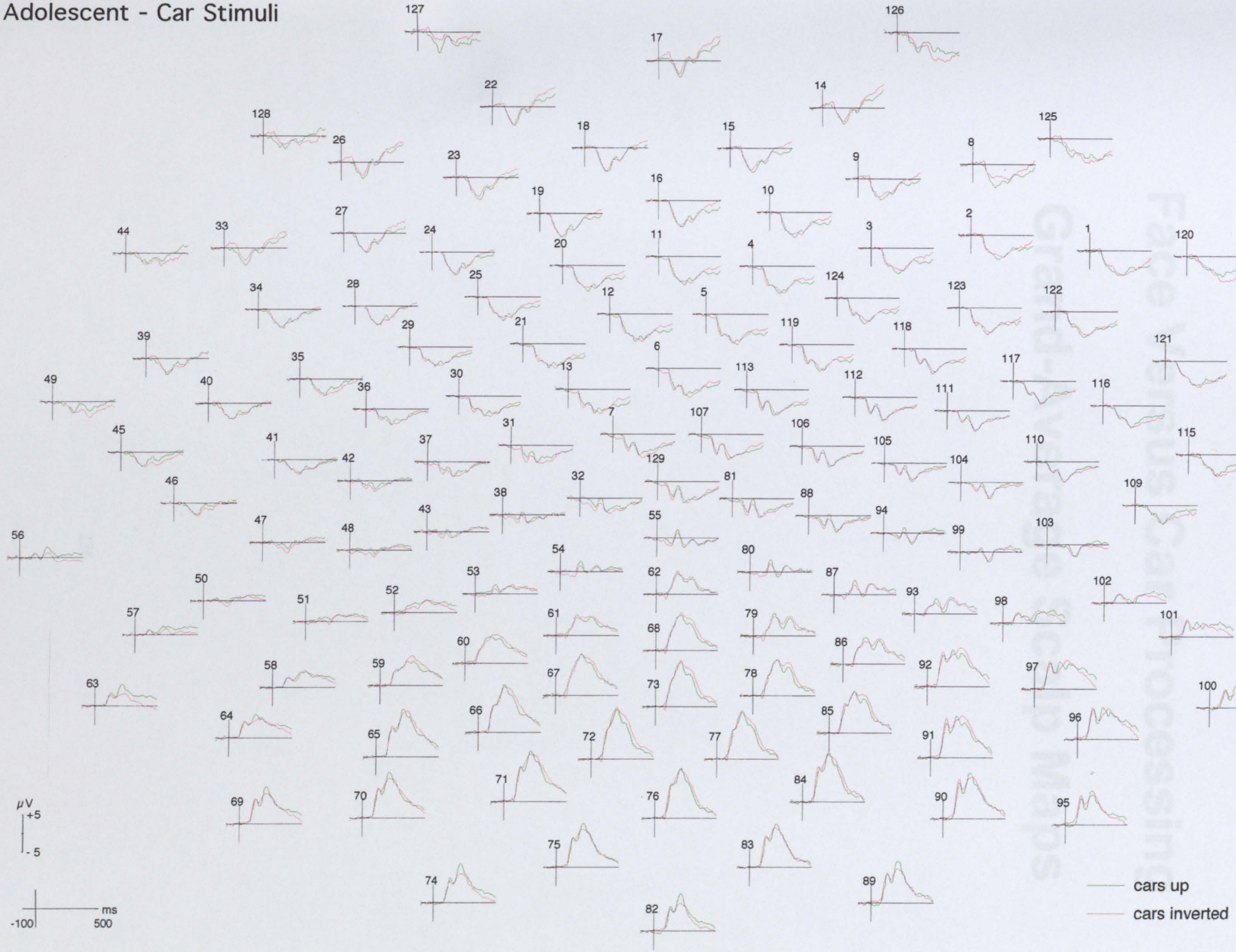


Control Adolescent - Car Stimuli



WS Adolescent - Car Stimuli



μV +5 -5

-100 ms 500

cars up

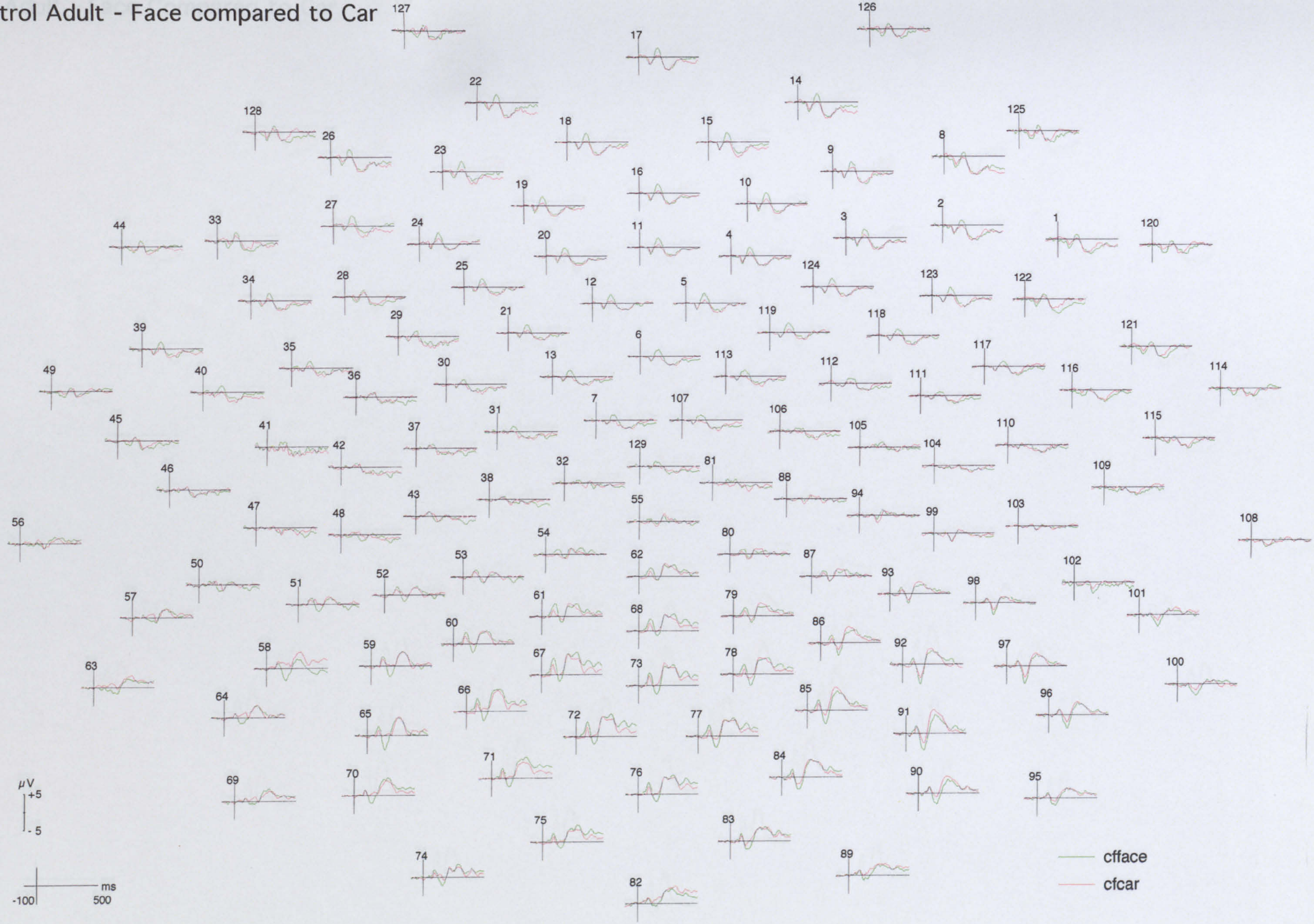
cars inverted

Appendix 3

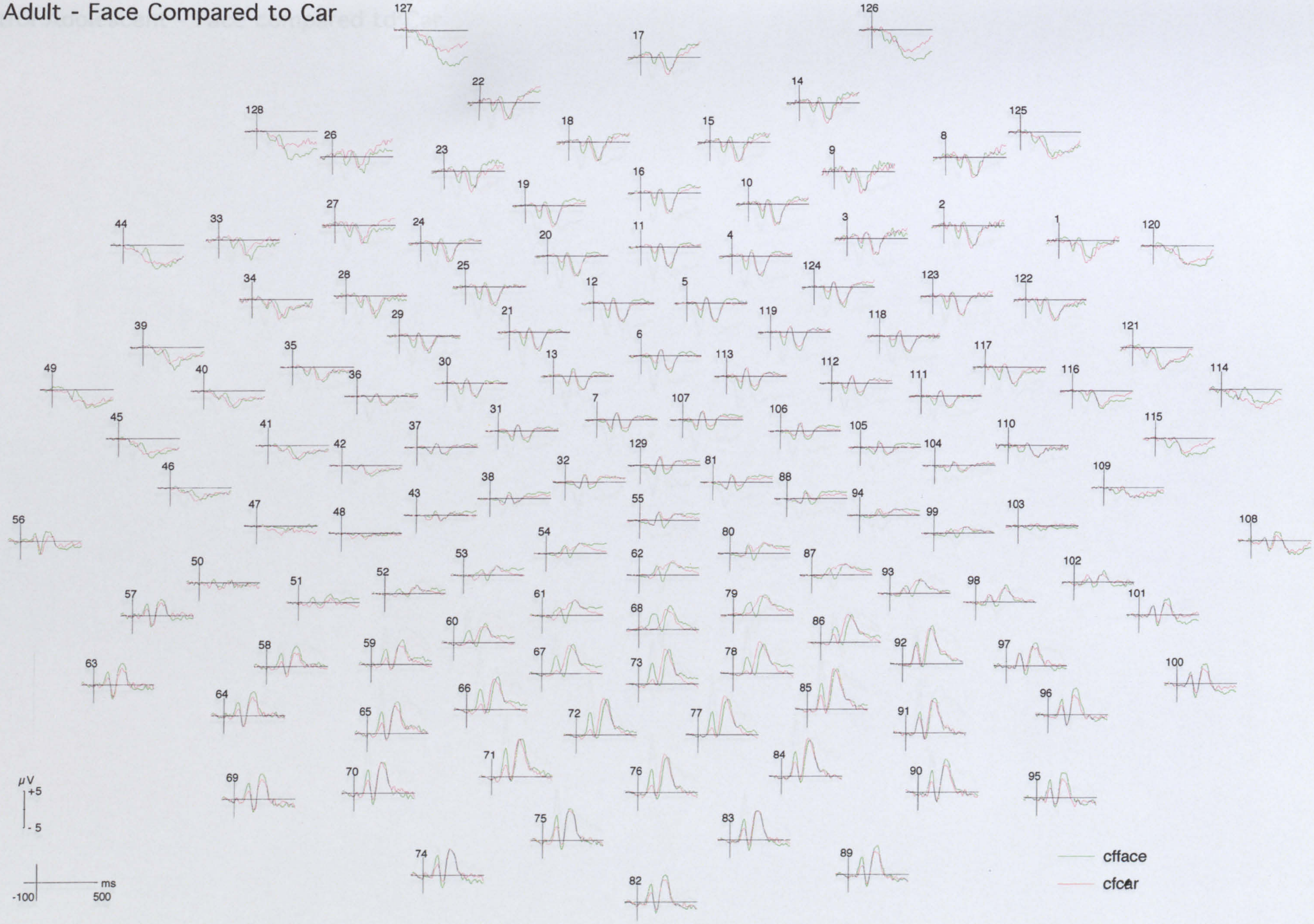
Face Versus Car Processing

Grand-Average Scalp Maps

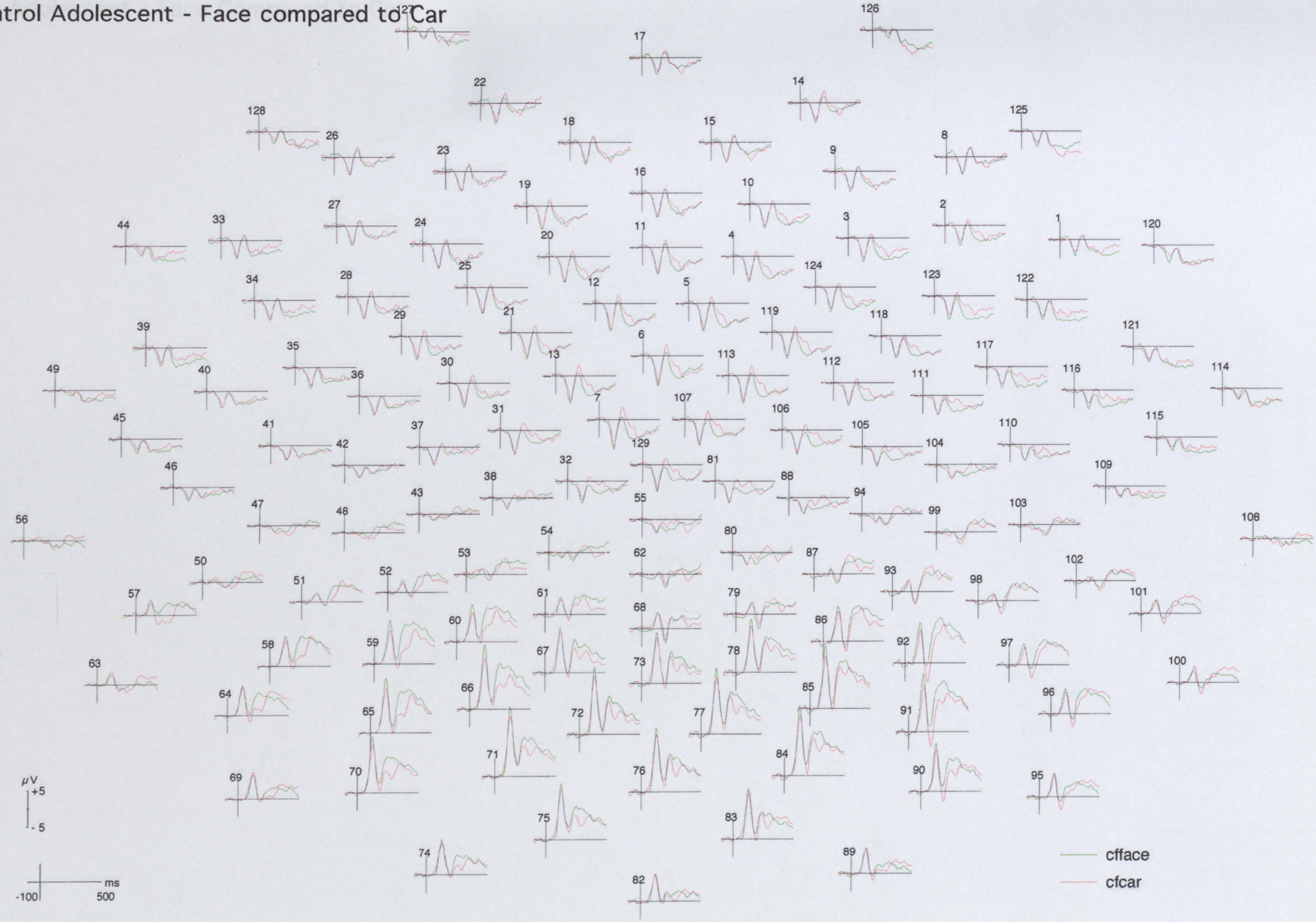
Control Adult - Face compared to Car



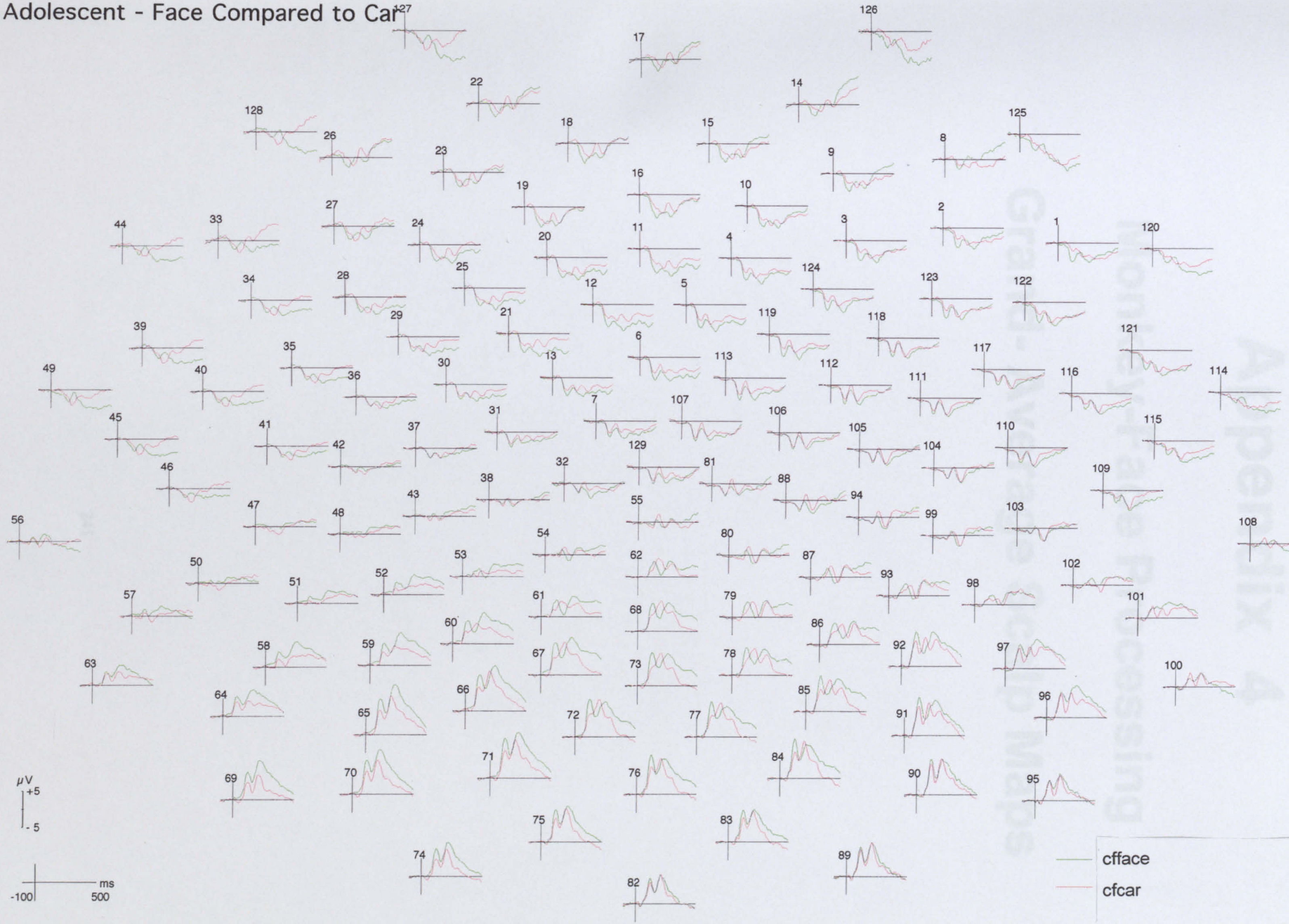
WS Adult - Face Compared to Car



Control Adolescent - Face compared to Car



WS Adolescent - Face Compared to Car



μV
+5
- 5

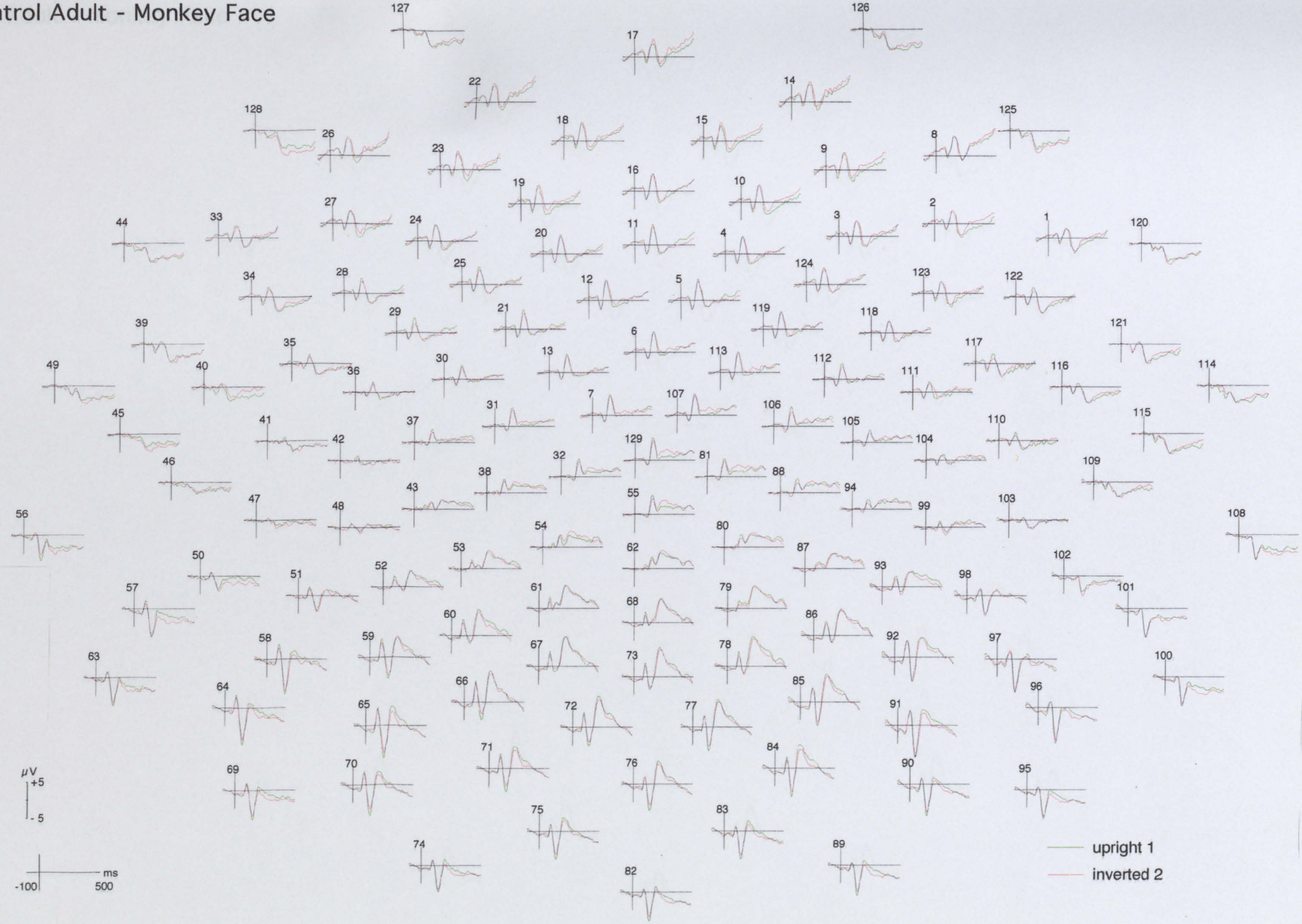
-100 ms 500

cfface
cfcar

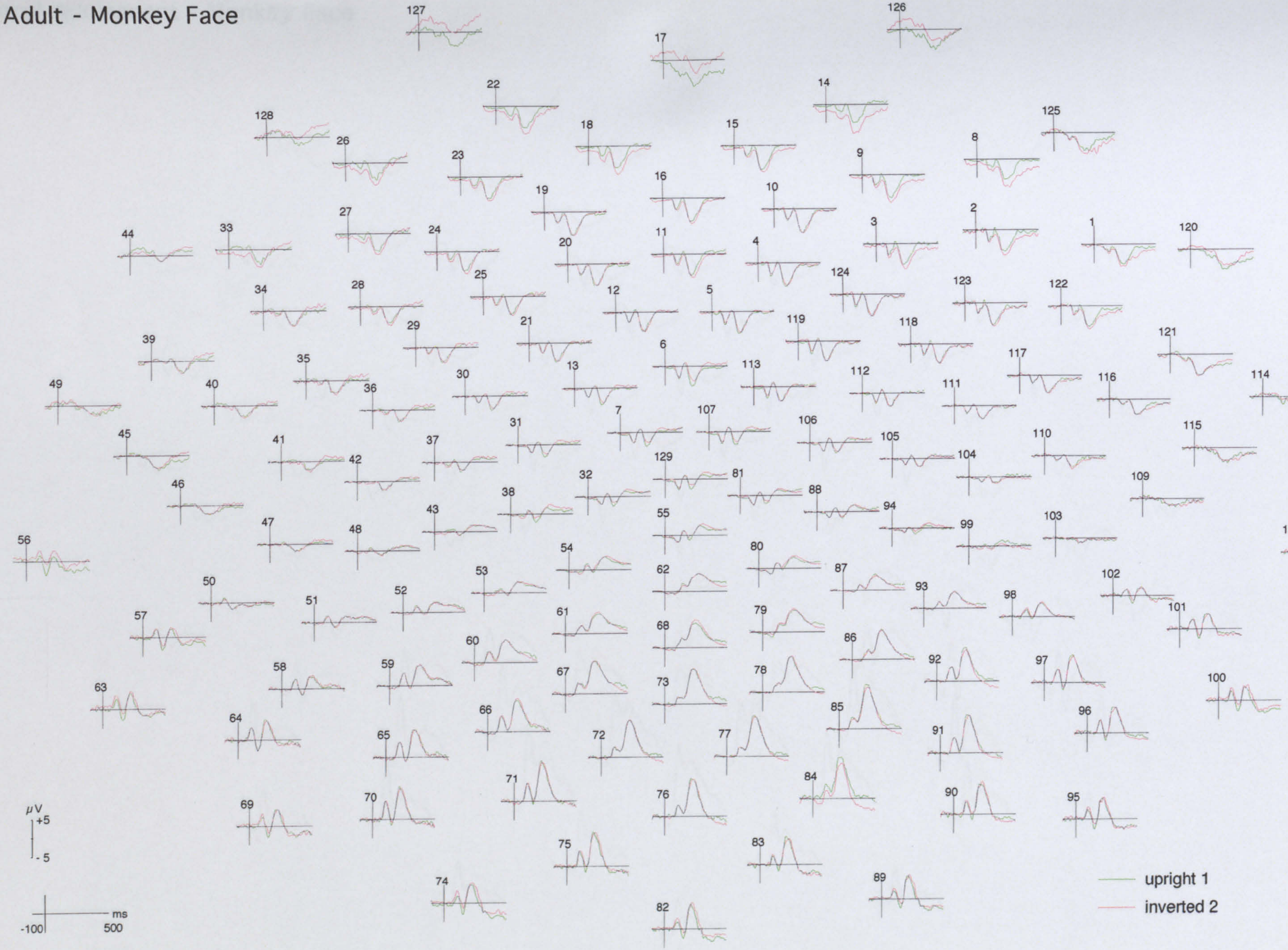
Appendix 4

Monkey-Face Processing

Grand- Average Scalp Maps


Control Adult - Monkey Face
μV
+5
- 5
ms
-100
500
upright 1
inverted 2

WS Adult - Monkey Face



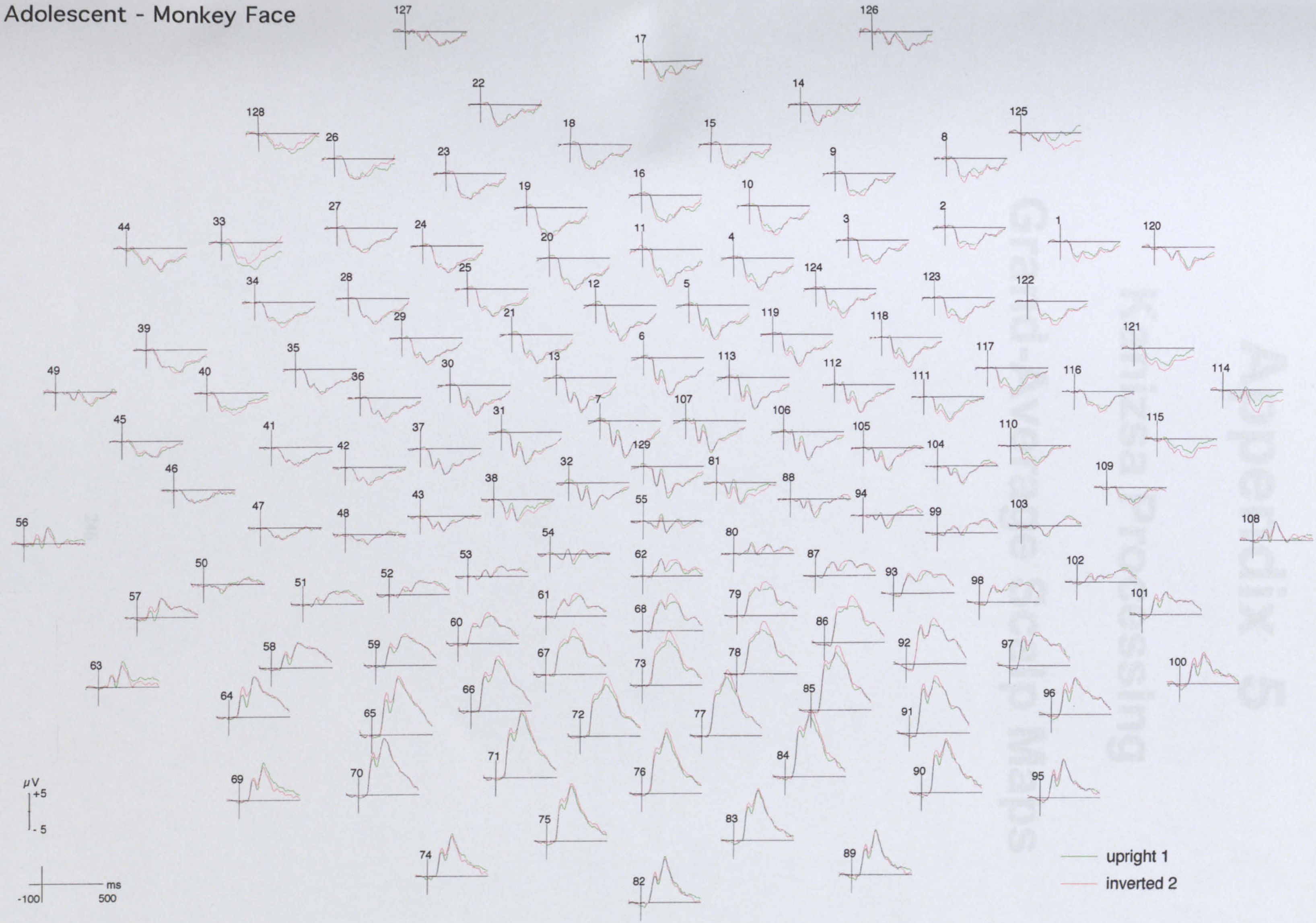
Control Adolescent - Monkey Face

μV
+5
- 5

-100
ms
500

upright 1
inverted 2

WS Adolescent - Monkey Face

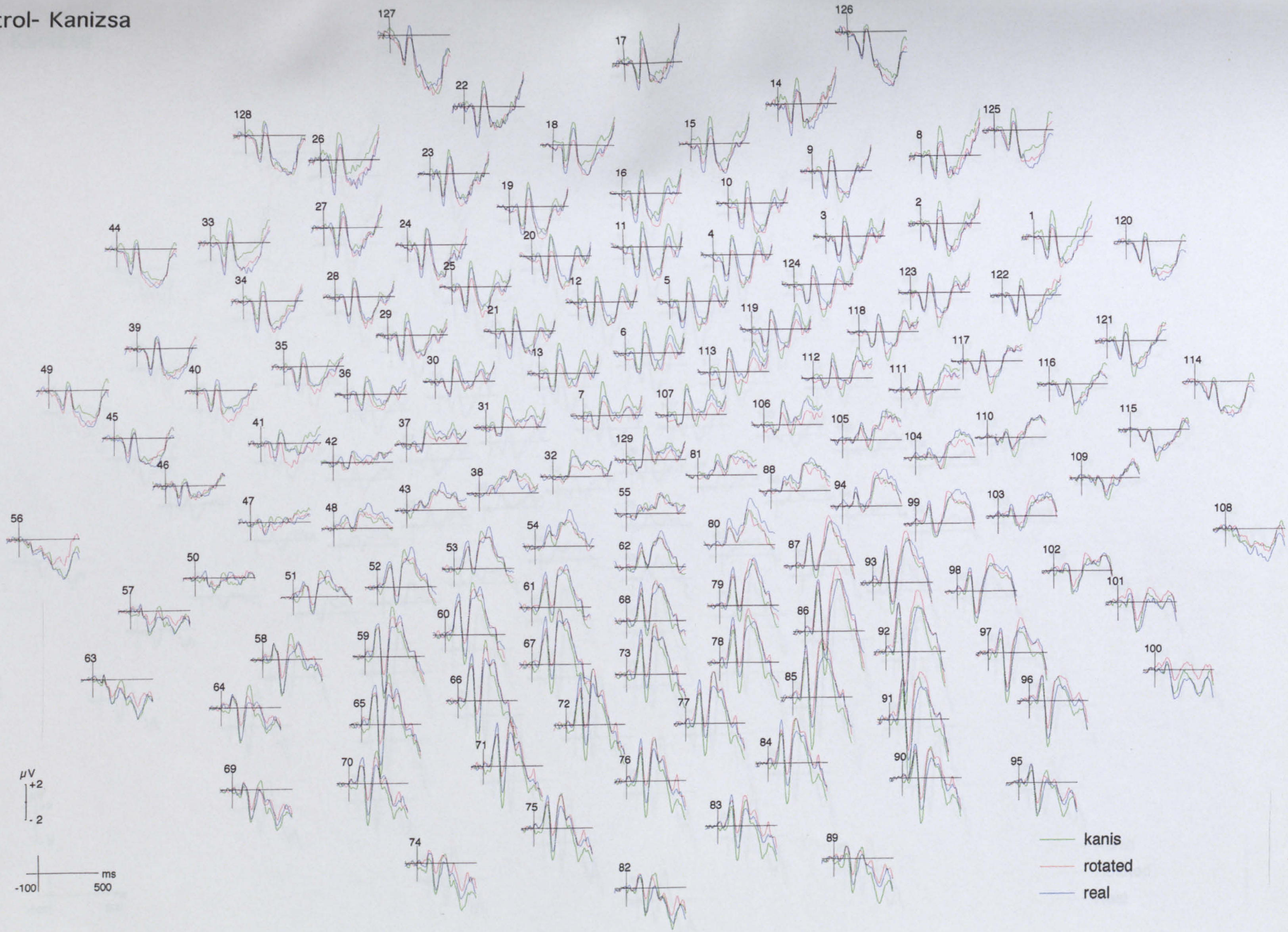


Appendix 5

Kanizsa Processing

Grand-Average Scalp Maps

Control- Kanizsa



WS - Kanizsa